Celso Gomes
Michel Rautureau *Editors*

Minerals *latu sensu* and Human Health

Benefits, Toxicity and Pathologies

Springer

Minerals *latu sensu* and Human Health

Celso Gomes • Michel Rautureau
Editors

Minerals *latu sensu* and Human Health

Benefits, Toxicity and Pathologies

Springer

Editors
Celso Gomes
Department of Geosciences
Researcher of the Research Unit
“GeoBioTec”
University of Aveiro
Aveiro, Portugal

Michel Rautureau
Docteur d’État ès Sciences Physiques
Retired of University of Orléans
Orléans, France

ISBN 978-3-030-65705-5 ISBN 978-3-030-65706-2 (eBook)
https://doi.org/10.1007/978-3-030-65706-2

The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2021
This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Humankind has used natural mineral resources for millennia, which have been central to the technological progress of human societies by providing mineral-based materials and their derivatives that shape the everyday lives of humans.

Human survival and development are dependent upon natural resources, water, land, forests, and minerals. Minerals are present, although not always very apparently, in every car, plane, bicycle, computer, TV set, cell phone, lamp, tile, brick, tableware, plaster, pigment, paper, cement, and glass. In fact, humans live side-by-side with minerals. Minerals are also present as fundamental constituents in the human body, as well as in pharmaceutics and cosmetics that humans use for healthcare and well-being. Minerals are essential to humans and other organisms and microorganisms.

This book is intended to be an updated and comprehensive academic review on both positive and negative interactions of minerals *latu sensu or* minerals *l.s.* regarding living quality for quality of life. As a rule, researchers do overweigh the negative interactions. On the contrary, this book seeks a harmonious balance of both categories of interactions.

To accomplish the main target of this book – a holistic approach to *minerals* and *humans* general and specific interactions – a broad concept of mineral was adopted, the concept of mineral *latu sensu* (mineral *l.s.*).

The comprehensive concept of mineral *latu sensu* (mineral *l.s.*) encompasses within other concepts presented ahead, the two most trivial: the concept of mineral *strictu sensu* (mineral *s.s.*) or mineral *itself* – natural, inorganic, solid, and crystalline product which is an important component of rocks and soils – adopted as so, for instance, in Earth sciences, soil sciences, and materials science; and the concept of *mineral* – chemical element of natural and inorganic origin, as a rule metal and metalloid, which is an important component of the human body, food (solid and liquid), and pharmaceuticals – adopted as so, for instance, in medical sciences, pharmaceutical sciences, and nutritional sciences.

All the chemical elements of natural origin and inorganic nature shown in the periodic table can be constituents of both *minerals s.s.* and *humans*. Also, very close relationships are known between *minerals s.s.* and *humans*. Both *minerals s.s.* and *humans* are chemical systems built with the same fundamental blocks – the natural chemical elements – although in different concentrations. Also, both *minerals* and *humans* follow processes of formation, growth, and duration, and sooner or later they disappear, since they are imperfect natural beings characterized by inherited and acquired defects and disorders. In *humans*, such defects and disorders could be expressed as diseases of more or less severity, imperfections that could be found in the genetic code. In *minerals*, such defects and disorders mean physical and chemical instability leading to alteration, transformation, and disappearance.

The general and comprehensive concept of mineral, the concept of *mineral l.s.* adopted in this book, allows to encompass the following particular concepts:

1. The *natural, inorganic, solid*, and *crystalline chemical elements* or *compounds* that participate: in the composition of rocks and soils, and can be present too dissolved or suspended in both mineral water and air; some of these minerals, particularly those suspended in respirable air and being either naturally or anthropogenetically produced, can cause serious diseases such as *silicosis* and *asbestosis* depending upon concentration and exposure duration in the respiratory system; other such minerals can play positive functions in *pharmaceutics* and *cosmetics.*
2. The natural, inorganic, solid, and crystalline compounds that undergoes man-made physical and chemical modifications, and is able to change, in a controllable mode, its natural physical and chemical properties assumed to be important for certain industrial applications, situation exemplified by the processes: delamination, intercalation, pillaring, and acid or alkaline activation being performed in certain clay minerals.
3. The bio-essential *chemical elements* of natural origin that, in the ionic form, are constituents of the solid food of either vegetable or animal nature being created in soil, which being named *macronutrients* or *mineral salts* and *micronutrients* or *oligominerals* are the main suppliers and carriers of minerals for human nutrition and wellness.
4. The *chemical elements* that in ionic form are constituents of potable mineral water which are currently called *minerals*, their decisive conditioning of human health and living quality being well established; mineral water that can be used for therapeutical purposes, for instance in *crenotherapy*, *hydrotherapy*, and *thalassotherapy.*
5. The *chemical elements*, also currently called *minerals*, which mostly enter as oligoelements into the formulations of the so-called *mineral supplements*.
6. The *nanominerals* characterized by nanosizes, exemplified by some types of *clay minerals*, which are actually investigated and used for the controlled and sustainable delivery of pharmaceutics.
7. The *biominerals* classified as either *bio-essential* for some human physiological systems such as bones and teeth, or *pathological* since they can cause pathologies such as *lithiasis* – urinary, salivary, renal, and biliary – due to the formation of the so-called *calculi* or *stone.*
8. The *special clays*, natural associations of minerals dominated by the so-called *clay minerals* – hydrous phyllosilicates – which are being used since Antiquity

as cosmetic products and as therapeutic materials in both internal and external applications, for instance those called *geophagy*, and *mud therapy*, and *pelotherapy.*

9. The hybrid mineral-organic complexes, such as clay-drug hybrid materials and clay-drug delivery systems, which are considered of paramount importance in the field of biomedical research and applications.
10. The *special sands*, such as those of biogenic carbonate minerals, those of radioactive minerals yielding radon gas evolution, and those of naturally heated volcanoclasts, which are used under the form of sand baths, either outdoors in the natural environment or indoors inside spa facilities in a therapeutic application named *psammotherapy.*
11. The *chemical elements* of natural and inorganic origin usually called *metals*; some could participate in the composition of *metalloproteins* and of *metalloenzymes* acting as catalysts in the health essential metabolic reactions; some others could be used too, for instance, in *disease diagnosis* and treatment in *cancer therapy.*
12. *Synthetic minerals* that can be used in pharmaceutics and cosmetics.

Very early on it is admitted that since the beginning of antiquity, man first empirically and much later on the basis of scientific principles and methods discovered that certain natural products, which later came to be called *minerals*, when ingested or applied topically had curative or healing effects on certain diseases of digestive and dermal conditions, such as alleviating ailments and gastric intoxications, healing wounds and stopping bleeding; some minerals could also have beneficial effects on skin care and treatment, both cosmetic and dermocosmetic.

It is well established that minerals participate in the constitution of all living beings and can condition the quality of the natural life support systems: soil, water, and the atmosphere. There are four sources for the human intake of minerals: food, soil, water, and air. Also, there are three pathways for the human intake of minerals: ingestion, inhalation, and skin absorption.

In humans, some minerals, depending on their bioavailability, can play three main positive roles:

1. Provide structuring in the formation of bones and teeth.
2. Help the maintenance of normal heart rate, muscle contraction and conduction of the nervous system, and acid–base balance.
3. Regulate cellular metabolism by being part of enzymes and hormones that control cellular activity.

Also, in humans, some minerals can play negative roles, which in certain circumstances can lead to pathological consequences, all caused by different exposure to potentially toxic minerals, the more or less severity of the pathologies mainly relying on both dose and exposure duration.

Humans have identified that certain minerals bearing lead (Pb) and mercury (Hg) can be the cause of diseases named *plumbism* or *saturnism* and *mercurosis* or *hydragirism*, respectively, which can be lethal. Progressively, humans found also that several diseases or pathologies are due to other minerals *s.s.* such as *silicosis*, *asbestosis*, *baritosis*, *siderosis*, *berylliosis*, and *talcosis*. Also, it became well established that mineral toxicity can be attributed to the excessive exposure to certain minerals in the elemental form as in the cases of As, Cd, F, and Se, which, being present in food and in drinking water, can cause the pathologies *arsenicosis*, *cadmiosis*, *fluorosis* and *selenosis*, the more or less severity of the pathologies being mainly related to both dose and exposure duration.

In general, minerals toxicity exposure involves processes that follow three pathways: ingestion, inhalation, and dermal absorption. Solid food of vegetable or animal origin and created in soil, as well as potable mineral water, are via ingestion the main suppliers/carriers of minerals in the elemental form for human nutrition and good or bad health.

In potable mineral water, which is essential for life, although condition of health quality depends upon its chemical and microbilogical composition, minerals are, as a rule, either dissolved in the elemental form (Na, K, Ca, Mg, Fe) or suspended in extremely fine particulate form (clay, oxides/hydroxides, organic matter).

Minerals l.s. are the fundamental constituents of the natural environment where humans live, and they use minerals for their survival and living quality. Naturally, both positive and negative interactions do occur between minerals and humans, and in the last two decades, the studies on these subjects have been dealt with within the sphere of action of the emergent scientific field called Medical Geology.

Research on medical geology in the search for relationships between the environment, the geologic environment in particular, and human health should involve a large number of areas of knowledge and specialties. Effectively, the diagnosis, prevention, and personalized treatment of a disease related to the geological environment can only be achieved through a wide interdisciplinary collaboration involving people with professional training in diverse scientific areas, such as medicine, geology, biology, biochemistry, biophysics, mineralogy, geochemistry, hydrogeology, hydrochemistry, ecology, environment, food chemistry, nutrition, toxicology, pathology, epidemiology, etiology, territory planning, and economics.

To be used by man, minerals require, first, to be extracted from the earth by mining and quarring processes, second to be submitted to physical and chemical processing. Mineral extraction, inherently irreversible and unsustainable, and mineral processing, as a rule, produce more or less serious impacts, both on the environment and on human health. For instance, underground water contamination caused by heavy metals and atmospheric contamination by metal-bearing dust are the major problems arising from mining and metallurgical processing. The rising public awareness of these impacts justifies the recycling, whenever possible, of mineral-based wastes.

In 16 chapters, this book intends to be a holistic approach to the knowledge, both historical and actual, of the benefits and hazards involving the diverse interactions between *minerals l.s.* and *humans*.

The aim of this book is to provide students and researchers worldwide with updated scientific data, generic and specific, of both positive and negative interactions of *minerals l.s.* on the *quality of life*. In fact, this book intends to gather, using an integrative mode, most of what is presently known of the significant contributions provided from various scientific and technological sources about the aforesaid interactions referred to. The scientific, historical, and technical references thoroughly disclosed in this book, although numerous, are certainly incomplete. Therefore, our best excuses for the missing references.

This book is particularly addressed to upper-level undergraduate, graduate, and postgraduate students and researchers doing studies and research, specifically in geological, biological, chemical, materials, environmental, pharmaceutical, and medical sciences.

The specific field of clay science being a subject of common interest to all the aforesaid sciences deserves a particular development in this book. Clay and clay minerals, within all minerals, and due to their ubiquity, diversity, and crystalochemical specificities, as well as to specific physical, chemical, and physicochemical properties, are the most acknowledged along the human history for various health benefits, first on an empirical basis, and later on a scientific basis.

Clay and clay minerals whenever used for therapeutics and cosmetics are currently part of formulations which are administered both orally and topically in various forms, such as patches, pastes, tablets, powders, capsules, emulsions, suspensions, creams, and ointments, and for such purposes, they had undergone little or much scientifically and technically sound processing and modification. However, particularly since the last decade and as output of scientific and technical developments, the so-called hybrid mineral-organic complexes, such as *clay-drug hybrid materials* and *clay-drug delivery systems*, are becoming matters of extensive biomedical research and application, either as formulation additives, or as drug carriers using a variety of routes, including oral, transdermal, and local administration.

Aveiro, Portugal
Orléans, France

Celso Gomes
Michel Rautureau

Citations

"We're well aware that every creative work is imperfect and that our most dubious aesthetic contemplation will be the one whose object is what we write. But everything is imperfect. There's no sunset so lovely it couldn't be yet lovelier, no gentle breeze bringing us sleep that couldn't bring yet sounder sleep."

Fernando Pessoa (1888–1935) – Portuguese poet, writer, and philosopher. *In*: *The Book of Disquiet*, Assirio & Alvim editors, 1st edition 1998.

"The poet Leopoldo Lugones affirms the friendship of man and stone. I want to refer to another more essential and mysterious friendship, the friendship of man and water. Most essential, because we are made not of flesh and blood, but of time, of fugacity, whose immediate metaphor is the water, and already Heraclitus of Ephesus has said so."

Jorge Luis Borges (1899–1986) – Argentine poet, writer, and philosopher. *In:* the book entitled *Atlas*, topic "As Fontes," Quetzal editors, 1st edition 2018.

"Let men, made up of flesh and blood, not complain about the brevity of life, for the stones also die, and also everything that has happened has passed, and everything that is passes too."

Padre António Vieira (1608–1697) – Portuguese preacher, writer, and philosopher. *In*: the book entitled *Antologia e Aforismos*, Telos editors, Porto, 1997.

"We only know exactly when we know little; as we acquire knowledge, doubt arises." "Knowing is not enough, we must apply." "Willing is not enough, we must do."

Johann Wolfang von Goethe (1749–1832) – German writer and scientist.

"Look deep into nature, and then you will understand everything better."

Albert Einstein (1879–1955) – German-born theoretical physicist and Nobel Prize winner.

Contents

Editors and Contributors

Editors

Celso S. F. Gomes Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal

Michel Rautureau Docteur d'État ès Sciences Physiques, Retired of University of Orléans, Orléans, France

Contributors

Francisco M. L. Amado Department of Chemistry, University of Aveiro, Aveiro, Portugal

Maria Helena R. Amaral Faculty of Pharmacy, University of Porto, Porto, Portugal

Ana Maria V. Cavaleiro Department of Chemistry, Inorganic Chemistry Group, University of Aveiro, Aveiro, Portugal

José A. S. Cavaleiro Department of Chemistry, Organic Chemistry Group, University of Aveiro, Aveiro, Portugal

Filomena V. Fernandes Physician, Expert in Public Health, Urbanização S.Luis, Faro, Portugal

João V. Fernandes AMTSBE (Association Mondiale de Tourisme de Santé et Bien-Être), Researcher and Consultant, University of Algarve, Faro, Portugal

Jorge H. C. Gomes Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal

Delfim F. G. Santos Faculty of Pharmacy, University of Porto, Porto, Portugal

Eduardo A. F. Silva Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal

João B. P. Silva Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal

Frederico J. Teixeira Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Chapter 1
Introduction: Targets and Concepts

Celso S. F. Gomes

Abstract It is known for centuries that minerals *latu sensu* (*minerals l.s.*) play decisive roles in both human health and living quality, naturally first on an empirical basis and later on a scientific basis. When ingested or applied topically, some minerals are reckoned for having curative effects on certain diseases of the digestive forum and dermal conditions, such as alleviating ailments and gastric intoxications, healing wounds, stopping bleeding, and skin care and treatment. In turn some minerals may be deleterious for the human health, even lethal depending on the exposure concentration and time. In the 16 chapters of this book, historical and scientific information, generic and specific of the positive and negative interaction of minerals in the human health, is disclosed. A holistic approach to these subjects is the main target of the book, and to fulfill this approach, a comprehensive concept of mineral has been adopted, the concept of mineral *latu sensu* (mineral *l.s.*) that has been presented in the Preface and thoroughly exemplified along this chapter.

1.1 Introduction: Targets and Concepts

This book is intended to be an updated and comprehensive academic review on both positive and negative effects of minerals *latu sensu* or minerals l.s. regarding human health and living quality. As a rule, researchers do overweight the negative interactions. On the contrary this book seeks a harmonious balance of both interactions.

To accomplish the main target of this book - a holistic approach to *minerals/humans* general and specific interactions -, a broad concept of mineral has been adopted, the concept of mineral *latu sensu* (*minerals l.s.*).

The comprehensive concept of mineral *latu sensu* (*minerals l.s.*) encompasses within other concepts ahead presented, the two most trivial: the concept of mineral *strictu sensu* (*minerals s.s.*) or mineral *itself* – natural, inorganic, solid, and crystalline product which is an important component of rocks and soils – adopted as so, for

---

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit "GeoBioTec",
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_1

instance, in Earth Sciences, Soil Sciences and Materials Science; the concept of *mineral* – chemical element of natural and inorganic origin, as a rule metal and metalloid, which is an important component of the human body, food (solid and liquid), and pharmaceuticals -, adopted as so, for instance, in Medical Sciences, Pharmaceutical Sciences and Nutritional Sciences.

All the chemical elements of natural origin and inorganic nature shown in the Periodic Table can be constituents of both *minerals s.s.* and *humans*. Also, very close relationships are known between *minerals s.s.* and *humans*. Both *minerals s.s.* and humans are chemical systems built with the same fundamental blocks – the natural chemical elements – although in different concentrations. Also, both *minerals* and *humans* follow processes of formation, growth and duration, and sooner or later they disappear since they are imperfect natural beings characterized by inherited and acquired defects and disorders. In *humans* such defects and disorders could be expressed as diseases of more or less severity, imperfections that could be found in the genetic code. In *minerals*, such defects and disorders mean physical and chemical unstability leading to alteration, transformation and disappearance.

The general and comprehensive concept of mineral, the concept of *minerals l.s.* adopted in this book, allows to encompass the following particular concepts of mineral:

1. The *natural, inorganic, solid and crystalline chemical element* or *compound* that participate in the composition of rocks and soils, and can be present too dissolved or suspended in both mineral water and air; some of these minerals, particularly those suspended in respirable air and being either naturally or anthropogenetically produced, can cause serious diseases dependent upon the exposure in the respiratory system, such as *silicosis* and *asbestosis*; other of these minerals can time play positive functions in *pharmaceuticals* and *cosmetics*;
2. The natural, inorganic, solid and crystalline compound which underwent man-made physical and chemical modifications able to change its natural physical and chemical properties with importance for certain industrial applications; such situation is well exemplified by cation exchange, delamination, intercalation, pillaring, acid or alkaline activation performed in certain clay minerals;
3. The bio-essential *chemical elements* of natural origin that in the ionic form are constituents of the solid food of vegetable or animal origin created in soil, which being named *macronutrients* or *mineral salts* and *micronutrients* or *oligominerals* are the main suppliers/carriers of minerals for human nutrition and wellness;
4. The *chemical elements* that in ionic form are constituents of drinking mineral water and currently called *minerals*, being well established their decisive conditioning of human health and living quality too; mineral water that can be used in therapeutics, such as *crenotherapy, hydrotherapy*, and *thalassotherapy*;

5. The *chemical elements*, also currently called minerals that enter mostly as oligoelements into the formulations of the so-called *mineral supplements*;
6. The *nanominerals* characterized by nanosizes, exemplified by some types of *clay minerals*, which are actually investigated and used for the controlled and sustainable deliver of pharmaceuticals;
7. The *biominerals* classified as, either *bio-essential* for some human physiological systems such as bones and teeth, or *pathological* since they can cause pathologies such as *lithiasis* – urinary, salivary, renal and biliar -, due to the formation of the so-called *calculi* or *stone*;
8. The *special clays*, natural associations of minerals dominated by the so-called *clay minerals* – hydrous phyllosilicates -, which are being used since the Antiquity as cosmetic products and as therapeutic materials in both internal and external applications called *geophagy, mudtherapy* and *pelotherapy*, respectively;
9. The *special sands*, such as: those of biogenic carbonate minerals, those of radioactive minerals yielding radon gas evolution, and still those of naturally heated volcanoclasts, which under the form of sand-baths are used, either outdoors in the natural environment or indoors inside Spas facilities, in a therapeutic application named *psammotherapy*;
10. The *chemical elements* of natural and inorganic origin usually called metals; some could participate in the composition of *metalloproteines* and *metalloenzymes* acting as calalysts in the health essential metabolic reactions; some others could be used too, for instance, in *disease diagnosis* and in *cancer therapy*;
11. *Synthetic minerals* that can be used in pharmaceuticals and cosmetics.

Very early, it is admitted that since the dawn of Antiquity, man first empirically and much later on the base of scientific principles and methods has discovered that certain natural products which later came to be called *minerals*, when ingested or applied topically had curative or healing effects on certain diseases of digestive and dermal conditions, such as alleviating ailments and gastric intoxications, healing wounds and stopping bleeding; some minerals could also have beneficial effects on skin care and treatment, both cosmetic and dermocosmetic.

The use of minerals for therapeutic purposes it is acknowledge since the earliest cultures, such as Ancient China, Mesopotamia (3000–2000 B.C.) with references on the famous Nippur clay plates or boards (~2500 B.C.), through Ancient Egypt with references on the famous *Ebers papyrus* (~1500 B.C.), Ancient Greece and Rome.

The plates or tablets of Nippur, Mesopotamia, listed clays as remedies for healing wounds and stopping the “body fluxes.” The *Ebers papyrus*, the world’s oldest medical text, listed clay as a mineral remedy for ailments such as diarrhea, dysentery, tapeworm, hookworm, wounds, and abscesses. Early also, still in antiquity, man discovered that some minerals, when extracted and processed from mines, could act as real poisons, naturally by inhalation of dust then generated [Hippocrates (460–355 B.C.) and Galen (131–201 B.C.)].

Poisoning caused by lead (Pb), mercury (Hg), and arsenic (As), called *plumbism* or *saturnism*, *mercurosis* or *hydrargyrism*, and *arsenicosis*, respectively, were common occurrences among the Romans.

By the Middle Ages, the illness caused by mineral dust was sufficiently recognized to be mentioned by Georg Bauer (1494–1555) whose pen name was the Latinized Georgius Agricola, in the book *De Re Metallica* published in 1556, in Latin, cataloging in 12 chapters labeled Books I to XII the state of the art of mining, refining, and melting metals. Georgius Agricola devoted his activities to study the relationships between mining and medicine.

The most poisonous minerals known in the Greek and Roman times were the minerals of *arsenic* (As), both *orpiment* (As_2S_3) and *realgar* (AsS), which could be lethal when inhaled. Solutions of these minerals, without smell and taste, were intentionally used as poisons. Later, it was identified that *mercury* (Hg) minerals and *lead* (Pb) minerals were equally strongly toxic.

Minerals and metals in particular are present in our daily lives, although the vast majority of us do not realize it. Really, we can't live without them. Within minerals the so-called industrial minerals and rocks, also called *non-metallic minerals* despite not being sources of metals, some are herein identified as aggregates (sand, gravel), clay (kaolin, bentonite, fibrous clay, ball clay, fuller's earth, heavy clay), limestone, dolostone, talc, feldspar, quartz, bauxite, asbestos, etc., participate in fundamental applications depending on their physical and chemical properties, in industries, such as construction, cement, ceramics, plastics, glass, refractories, paper, paints, rubber, fertilizers, pesticides, absorbents, cosmetics, pharmaceuticals, etc. (Kogel and Trivedi 2006). Other minerals, the so-called metallic minerals, are the source of metals, some herein identified: iron ores, copper ores, gold ores, zinc ores, rare-earth ores, etc.

As a matter of curiosity it is interesting to know that in the manufacture of a "smartphone," a machine or commodity so common and important these days, 40 metals are utilized. In a smartphone, the major metals are Cu (13.7 g), Ag (0.189 g), Au (0.028 g), and Pd (0.014 g). In 2015, Samsung produced 83.2 million smartphones, and Apple produced 61.2 million smartphones, which required 7913 tons of copper and 16 tons of gold. Other eight essential metals (Y, La, Ce, Pr, Nd, Gd, Tb, and Dy) belonging to the so-called group of rare-earth elements (REEs) commonly referred to as lanthanides, which are characterized by unusual physical and chemical properties, in particular magnetic and optical properties, are utilized in a smartphone. Some REEs are essential to the manufacture of smartphones, tablets, and computer flat-panel screens, and also in computers hard disk drives, special alloys, fluorescent and LED lightings, catalytic converters, medical imaging devices, etc.

There are 15 REEs which are classified into two groups: light REEs (La, Ce, Pr, Nd, Sm, Eu, and Gd) and heavy REEs (Tb, Dy, Ho, Er, Tm, Yb, Lu, and Y). The REEs commonly occur together in the Earth's crust in carbonatites, alkaline igneous rocks, ion adsorption clay deposits, and monazite-xenotime-bearing placer deposits.

Magnets based on Nd-Fe-B are the strongest permanent magnets so far known. Ce and La are being investigated as anticancer agents. A review of REE applications, occurrence, exploration, and environmental impact can be found in USGS (2014) and Balaram (2019). Actually, REE market supply is much dependent on China (controls 95% of the global market, southern China being the world's primary source of REEs, extracted from ion adsorption clay deposits); the reason why REEs are "critical" or "strategic" mineral resources is its high potential of supply-side risk or supply vulnerability (Elements v.8 (5), 2012; Géochronique Juin 2008). Presently, besides REEs, other minerals in the elementary form such as lithium (Li) and cobalt (Co) are considered "critical" too.

Material science, minerals and their derivates included, and health sciences are presently within all sciences, the most relevant and productive, both scientifically and technologically. Some metals and metalloids, even as trace elements, are being used in some of today's most sophisticated medical applications.

Actually, the decarbonation of the global economy – required by the so-called climate crisis – and the new wave of technological evolution featuring artificial intelligence (AI) and 5G networks fuel the race to secure uninterrupted access to critical minerals. Electrification is seen as the way forward for various sectors. Transportation – responsible for over 20% of the global emissions during the last decade – is expected to transition to alternative energy vehicles with expanding share of electric vehicles (Evs). The push toward Evs seems unstoppable. The Netherlands has pledged to ban the sale of petrol and diesel cars by 2025, and the UK and France by 2040. China is targeting zero-emission cars as 12% of new car sales by 2020.

Since the beginning of the twenty-first century, the production of lithium (Li), metal indispensable to high-tech, green economy and the defense industry, began to grow rapidly in order to meet the demand for lithium-ion batteries. However, Li resources are highly concentrated in South America, especially in Argentina (14.8 million tons), Bolivia (9 million tons – of largely untapped resources), and Chile (8.5 million tons). Because of their dominant position, these three countries have become known as the "lithium triangle" (Kalantzabos 2019).

According to the *Portuguese Mining Bulletin – Special Edition Lithium* (2017–18), Portugal is the EU country with the largest lithium reserves concentrated in the northern and central areas, Li mainly occurring in the minerals *spodumene*, $LiAl(SiO_3)_2$, and *lepidolite*, $Kli_2Al(Si_4O_{10})(F,OH)_2$.

Cobalt (Co) is also a key metal and ingredient in batteries for smartphones, laptops, and electric cars. However, the dominant producer is the Democratic Republic of Congo, which currently accounts for more than 60% of the world's cobalt mine production and boasts by far the largest reserves in the world.

The discovery of metals, naturally extracted from certain minerals, was a key factor for the development of civilizations and the establishment of the first empires by military forces. The metals copper (Cu) and tin (Sn) were the first metals used by man who, as soon as he knew how to produce the alloy called bronze, made it possible to manufacture efficient tools to use in agriculture, and at the same time lethal weapons. Small groups of men with bronze swords succeeded in defeating armies armed with pieces of stone, bone, or stick. Later, in the East, around the thirteenth century B.C., metallurgical techniques allowed the production of iron armaments, resulting in a new civilization leap that in Europe was only felt many centuries later. The civilization leaps due to the discovery of bronze and iron were equivalent to the civilization leap that many centuries later had been due to the discovery of gunpowder and firearms.

The increasing concern of modern societies with the interactions between the environment and health, in particular through the geological processes and products, justified the emergence in the last two decades of the scientific field called "Medical Geology," mainly focused on the negative or hazardous effects of minerals themselves and natural chemical elements, despite their fundamental and paramount importance for both good health and living quality.

Duffin et al. (2013), Duffin (2017), and Hoch (2017) show the historical connections between geology and medicine. Duffin (2017) produced a brief but concise historical backdrop on the historical links between medicine and geology initiated with a reference to the *Dictionary of Assyrian Chemistry and Geology*, in which Claredon Thompson (1936) mentions 120 mineral drugs cited in the clay tablets excavated from the King Ashurbanipal of Assyria's Library, at Nineveh, and whose links continued with references to the contributions of the Egyptian, Greek, Roman, Arabic, and Medieval and Renaissance schools.

Within the first minerals utilized by man for curative purposes, it should be enhanced the so-called medicinal earth or medicinal terra (*terra* from Latin), also known as *terra sigillata* or *terra sellada,* particularly exploited in certain volcanic islands of the Aegean Sea. *Medicinal earth* was commercialized and utilized since the antiquity up to the eighteenth century. Each one of those islands produced its own *medicinal earth* named according to its provenance: *Lemnian earth* from the Lemnos's island; *Cimolian earth* from the Kimolos's island; *Samian earth* from the Samos's Island; and *Melos* or *Milos earth* from the Melos's or Milos's island.

Lemnian earth, a famed medicine from antiquity to post-Medieval times being used as an antidote to snake bites or to any poison internally taken and to cure ulcers and dysentery, was firstly used in the Greek island of Lemnos in around 500 B.C. The clay torches were crushed into a powder and taken with liquids or made into paste and smeared on parts of the body. The worldwide increased demand inspired a host of counterfeits and imitations. The need of an increased supply leads to the survey of new sources of similar medicines, which particularly in Medieval and post-Medieval times were discovered, prepared, and commercialized in Hungary, France, Germany, Malta, Sienna, and Silesia.

With the progressive evolution of the knowledge acquired by man, he came to know that the *medicinal terra* is a geological material to which was given the name of clay. Some types of clay, to which were already recognized in the twentieth century, specific medicinal properties and functions and scientific and commercial names too, as well as other pharmacological preparations based on *minerals*, have been included in pharmacopeias, from the first that appeared in the sixteenth century to the contemporaneous ones, as active substances or as excipients, in one case and another with different functions. As a rule, the therapeutic activity of clay takes place by oral and topical pathways. Orally the following functions are highlighted:

gastric anti-acidity, gastrointestinal protection, anti-diarrheal, antianemic, laxative, homeostatic, and dietary supplementation.

Geophagy, particularly through ingestion of the so-called edible clays, is a good example of the internal use of minerals for curative purposes. The internal uses of minerals, *clays* and *clay minerals* in particular, and their benefits and risks will be disclosed in this book.

Topically, the following antiseptic, anti-inflammatory, disinfection, dermal protection, and sun protection functions of minerals are highlighted. *Mud therapy* and *pelotherapy* are good examples of the external use of curative minerals in the form of poultices, patches, and facial masks. The topical uses of minerals, clays and clay minerals in particular, and their benefits and risks will be also disclosed in this book.

Today we know that *minerals* and the *human body* are chemical systems which have in common many of their elemental constituents, the natural chemical elements, classified as metals, metalloids, and gases. Life, living beings, and biodiversity much depend on the relationships that could be established and developed between these elemental chemical constituents. Therefore, the development of Pharmacology has been parallel to the development of Chemistry and also to the development of therapeutics as a competence of medicine.

Evolution has been so remarkable that presently in many pharmaceutical formulations, the minerals as natural products have been replaced by the so-called synthetic analogs produced in laboratories and industries even though from natural products (minerals included) but having improved properties, for example, the degree of purity. Naturally, the participation of *minerals* in pharmaceutical formulations requires them to undergo previous industrial and laboratory processes used in the so-called pharmaceutical technology.

Today we also know that *minerals*, in the broad concept of mineral *latu sensu* (*mineral l.s.*), term adopted in this book, occur in the whole natural environment:

1. In rocks and soils, both in the form of mineral itself, that is, as natural, inorganic and crystalline solid, considered *mineral stricto sensu* or *mineral s.s*, and in the elemental free form, considered the *chemical element* of natural origin constituting the *minerals s.s.*, and which in the natural environment occur either solvated or fixed to the surfaces of inorganic and organic compounds;
2. In mineral waters, dispersed and suspended in a colloidal form of the *mineral itself* or *mineral s.s.* (it is the case of nanoclay), and/or in a solution in the elemental form;
3. In the air, dispersed in the form of *mineral itself* or *mineral s.s.*, and/or in the elemental free form or fixed to aerosols.

The concept of mineral *latu sensu* or mineral *l.s.* encompasses the two aforementioned forms, natural inorganic and crystalline solid and natural solid chemical element. Minerals in the natural environment can occur in these two forms. We well know that the names of some natural inorganic and crystalline solids and natural elements sometimes coincide; they are the cases, for instance, of *gold* (Au), *silver* (Ag), *copper* (Cu), *iron* (Fe), *sulfur* (S), and *carbon*-I, the so-called native element minerals.

The mineral forms referred to as the natural chemical elements can occur free and dispersed in rocks, soils, water, and air. Also, in this book, the concept of mineral *l.s.* comprises too some natural associations of minerals *s.s.*, as are the cases of certain types of *clay* to which man since the antiquity had recognized their healing properties.

Mineral water from the surface or from underground reservoirs and used for human consumption is itself essential for life due to the "minerals" it contains dissolved and in the elemental and ionic form, as cations and anions. Such justifies the generalized designation "mineral water."

There is general and specific information on the historical evolution of the use and effects, both positive and negative, of minerals on the human health. Information exists too on the sources – food, water and air, and pathways – ingestion, inhalation, and dermal absorption, which rule the availability and the incorporation of minerals in the human body, and supplemental information exists on the application and function of minerals in terms of human health, exemplified as follows: Campbell Thomson (1936); Duffin (2013); Gomes (2003, 2012, 2013, 2015a, b, 2017); Gomes and Silva (2003, 2006, 2007, 2010a, b, c, 2012); Hall and Photos-Jone (2008); Macgregor (2013); Photo-Jones et al. (2017); Rautureau et al. (2010, 2017); Retsas (2016); Teixeira (2009, 2016); Viseras et al. (2019).

All natural and inorganic chemical elements or "minerals" are present in the human body, and a significant number of them reckoned as essential to human health are classified as major, minor, and trace elements. Such elements could be good, tolerable, or toxic for human health depending on the individual dose. In particular, *mineral toxicity* due to dose excess or deficit will be enhanced. Also, minerals *s.s.* whether present as fine particles suspended in the air that is inhaled can cause severe pathologies, such as *silicosis*, *asbestosis*, *siderosis*, and *talcosis*.

Information about the use of some *minerals* as active substances and as excipients in pharmaceuticals is disclosed, the use of those *minerals* being dependent upon their specific crystallochemical properties.

As active substances in pharmaceuticals, *minerals* can perform important specific functions, such as gastric antacid, gastrointestinal protection, anti-diarrhea, laxative, antianemic, antiseptic and disinfectant, dermatological protection, solar protection, cosmetics, abrasive and mitigator of dental sensitivity, ocular congestion relieve, nutritional supplement, means of diagnosis and treatment, immobilizer in orthopedy and mold in odontology, contrasting mean in pathology diagnosis, and hemostatic agent.

In turn, as excipients in pharmaceuticals, minerals play the following main functions:

1. Improvement of organoleptic properties (taste and color);
2. Improvement of physicochemical properties (viscosity, dispersibility, suspendability, and thickness);
3. Facilitation of preparation and conservation of formulations (dilution, lubrication, and desiccation);

4. Facilitation of the release of the active drug ingredient in a particular site inside the organism.

Also, as excipients, minerals perform important specific functions, such as lubrication, taste correction, disintegration, dilution, binding or aggregation, pigmentation, emulsifying, thicknessing, and carriers for the controlled release of drugs.

Yet, there is significant information about the minerals utilized in cosmetics. In the manufacture of cosmetics, thousands of chemicals can be used. A typical cosmetic product could contain anything from 15 up to 50 ingredients. Most cosmetics contain a combination of at least the following functional ingredients: water, emulsifier, preservative, thickener, emollient, color pigment, fragrance, and pH stabilizer.

Also, interesting information exists on *metals*, natural elements constituents of the Earth's crust which are released from *minerals s.s.*, some of them that, in small amounts, are needed in the human body participating in the composition of *metalloprotein*s (generic term for proteins that contain metal ions as cofactors) and *metalloenzymes* (enzyme proteins that contain metal ions as cofactors), both fundamental for life and health.

In the Earth's crust, there are, in the native state, near 30 chemical elements, mainly metals, few being metalloids and gases. Native elements, native metals, and native metalloids can occur as native *minerals s.s*. The chemical native element or native metal iron (Fe) forms the native mineral α-Fe named *ferrite*. This example could be extended to the native metals Co, Ni, Pt, Ir, Pd, and Rh of group VIII in the Mendeleev's table, to the metals gold (Au), silver (Ag), and copper (Cu), to the metalloids As, Bi, and Sb of group V, and yet to the metalloids S, Se, Te, and C (native minerals *diamond* and *graphite*) of group VI.

Metals are of paramount importance for human health. For instance, the metal iron (Fe) is a constituent of hemoglobin; the metals copper (Cu), zinc (Zn), and manganese (Mn) are constituents of enzymes; and the metal chromium (Cr) is a cofactor in the regulation of sugar levels. Some other metals, as are the case of the so-called heavy metals, such as lead (Pb), cadmium (Cd), and mercury (Hg), can be deleterious to human health.

Metals can be intake from environment by organisms, man included, through ingestion of water, solid food, and plants. Metals can be taken from the environment by plants, through the roots and leaves. Metals can be taken from inhalation of dusts, gases, and aerosols. Metals can be bio-accumulated up the food chain. Therefore metals, those good or bad for human health, are included in this book into the concept of *mineral latu sensu* (*mineral l.s.*). Still regarding the *concept of mineral*, it is important to note that the concept varies from the Earth Sciences to the Pharmaceutical Sciences, to the Medical Sciences and to the Nutrition Sciences.

"Inorganic solid whose constituent chemical elements have their own ordered organization, and that is formed in the natural environment without human intervention" – this is the concept of *mineral* adopted by the specialists in Earth's Sciences, Materials Science, and Soil Science, and corresponds to the concept of *mineral stricto sensu* (*mineral s.s.*). The proper three-dimensional and ordered organization of the chemical element constituents of minerals is specific to the so-called natural crystals, and almost all *minerals s.s.* are *natural crystals*.

Otherwise, the specialists in Medical Sciences, Pharmaceutical Sciences, and Nutrition Sciences, in general, call minerals "The chemical elements of natural and inorganic origin that are essential to man's life and quality of life." However, it should be noted that in Pharmaceutical Sciences, the concept of *mineral* is effectively double, covering the aforementioned chemical elements and some natural inorganic solids, the latter being part of the so-called active substances and excipients, both components of the so-called pharmaceutical formulations.

Also, in the Medical Sciences, in addition to the chemical elements above recalled, the mineral designation is also applied to the so-called biominerals formed in the human body by cell division, and which are both *bio-essential* (constituents, for instance, of the bones and teeth) and *pathological* (constituents, for instance, of kidney stones and gallstones). And, it is well known that minerals participate in the constitution of all living beings and that they condition the quality of the natural systems which are life supporting: soil, water, and atmosphere.

In humans, *minerals* play three main roles:

1. Provide structuring in the formation of bones and teeth;
2. Help in the maintenance of normal heart rate, muscle contraction, conduction of the nervous system, and acid/base balance;
3. Regulate cellular metabolism by being part of enzymes and hormones that control cellular activity.

Minerals can also have deleterious effects on humans. It is known that a good part of the human diseases is related to the minerals of both geogenic origin and anthropogenic origin present in the natural environment that serves as habitat for the man. It is well-acknowledged that some diseases are related to lifestyle, others are due to the action of pathogens (viruses and bacteria), and several others are genetically dependent. Also, it has been effectively demonstrated that in the natural environment man's exposure to certain geological materials and processes can be a cause of disease, some of which can be lethal, for example, excessive exposure to certain potentially toxic natural elements such as arsenic, lead, cadmium, mercury, selenium, fluorine, uranium, and radon, which may be present, either in the soil particularly affixed to clay particles and utilized by the plants which are at the base of the food chain, or in the water, or yet in the air.

The importance of the so-called nanominerals and nanomaterials in Pharmacy and Therapeutics will be dealt with in this book. *Nanominerals* also play important functions in the field of *nanomedicine* defined as the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body.

Nanomedicine embraces five main sub-disciplines which are in many ways overlapping and are underpinned by common technical issues: *nanomaterials and devices*, *analytical and imaging tools*, *novel therapeutics and drug delivery systems*, *clinical applications*, and *safety and toxicological issues* (*environmental*, *manufacturing*, and *clinical use*) (ESF-European Medical Research Councils report, 2004). Nanominerals such as *carbon nanotubes*, *halloysite nanotubes*, *allophane*, and *imogolite nanospherules* and *tubules* have been thoroughly investigated as drug delivery systems. Also, minerals ever since have been used in cosmetics, and currently under the form of *nanominerals*, they are incorporated in several cosmetic products, such as creams, powders, emulsions, sunscreens, lipsticks, bathroom salts, and toothpastes.

Experience shows how important are the roles of *clay* and *clay minerals* for human health, the reason why one chapter of book is dedicated to clays and clay minerals and to their crystallochemical properties that could justify both positive and negative interactions on human health. Clays are one of the oldest earth materials used for healing purposes in the traditional medicine, and they continue to be applied in modern life for the treatment of various topical and internal ailments. Effectively clays are mineral resources and not *minerals s.s.* As a matter of fact, clays are aggregates of different minerals, which as a rule have associated non-mineral substances, such as organic matter and amorphous iron oxyhydroxides. Clays and clay minerals can be used *unmodified* (natural or synthetic) or *modified* (composites such as *clay-drug hybrids*, *organoclays*, *clay-polymer hybrids*, and *hydrogels*).

Nanostructured materials can be produced by the intercalation of organic molecules, such as proteins, enzymes, peptides, carbohydrates, nucleic acids, lipids, and polymers, within the interlayer spaces or other internal spaces of clay mineral structures, taking advantage of clay minerals' specific physicochemical properties, such as high specific surface area, electric charge, and reactivity.

Smectite clay minerals (*montmorillonite* and *hectorite*), fibrous clay minerals (*palygorskite* and *sepiolite*), and kaolin clay minerals (*kaolinite* and *halloysite*) are the mineral species most utilized in biomedical and pharmaceutical applications. *Biomolecules*, either negatively or positively charged, can be immobilized, stabilized, and preserved on the basal and edge surfaces, or in interlayer spaces or micro-channel spaces of clay mineral particles.

Experience has shown how positive, important, and unique is the role of certain natural or modified clay minerals in controlled drug release systems, as well as in the field of biosensors (e.g., *enzymatic biosensors*) and in the field of *regenerative medicine* or *regenerative tissue engineering*.

New trends on developments of controlled drug release based on clay-drug hybrid systems take into account the kind of administration route (oral, topical, transdermal), hoping to be deployed to specifically targeted parts of the human body (organs or cells). In general, clay-drug hybrid systems seemed to be very effective and to work well in vitro, and not so well in vivo. Hence, some challenges still remain for researchers.

Great advances are being made in the field of polymer nanocomposites based on both clay and clay minerals for various applications in automobiles, packaging, aerospace, and agriculture sectors. The required modification of clay particles involves the application of physical and/or chemical methods, always aiming at the achievement of stronger interaction among clay particles and modifying agents. The so-called organoclays, obtained by intercalating some organic molecules into the structure of certain clay minerals, particularly in those belonging to the smectite group, have promising potential on the biomedical and pharmaceutical fields of application.

In the biomedical field of applications, clays are used in pharmaceutics (both as active ingredients in the case of drug carriers and as excipients), cosmetics (sun screens and topical care), biomaterials (scaffold, hydrogel, foam, film), biosensors (electrochemical), and medical devices (patches, implants, medical plastics). In fact, recent research reinforces the promising potential on the biomedical and pharmaceutical fields of application.

As active substances or ingredients, to certain types of natural clay of green or blue colors that bear reduced transition metals such as Fe^{2+}, Cu^{2+}, and Zn^{2+}, are being attributed bactericidal properties, and in the last decade, the significant investigation being carried out has confirmed such properties relative to various pathogenic bacteria and has tried to identify the mechanism of the microbicide action and to establish the methodologies for both internal and external (topical) applications. Clay bactericidal character does not exist if clay is in the dry state – only when clay is in the hydrated state, for instance, in the paste state, microbicide action exists. Such microbicide action creates high expectations when both public health and science are becoming more and more apprehensive and engaged relatively the increasing resistance of bacteria to antibiotics.

Specific clays and clay minerals have proved to be valuable in the treatment of bacterial diseases, including infections for which there are no effective antibiotics, such as *Buruli ulcer* disease caused by *Mycobacterium ulcerans*, and multi-drug resistant infections. Dozens of scientific articles can be found in the literature describing and investigating the mechanisms of action of the so-called killer clays, which can be a possible new answer to "superbug" infections. "Superbugs" are pathogens or disease-causing microorganisms resistant to multiple antibiotics, and such antibiotic resistance is presently a matter of major public health concern. One example of "superbug" is the methicillin-resistant *Staphylococcus aureus* (MRSA). "This serious threat is no longer a prediction for the future," states a World Health Organization report. "It's happening right now in every region of the world and has the potential to affect anyone, of any age, in any country."

Topical antimicrobial therapy emerges as an attractive route for the treatment of infectious diseases due to the increased resistance to oral-administered systemic antimicrobial therapy (Lam et al. 2018).

Microbes are essential components of most environments on Earth, being present for instance, in the geomaterials, such as soils, clays, and mineral waters. Minerals provide microbes with nutrients, energy, and livable habitats, and microbes intervene in mineral weathering and diagenesis through their effects on mineral solubility. By contrast, microbes can form *minerals* as a by-product of either their surface reactivity toward soluble metals or as a consequence of their metabolism. The so-called microbiome is an essential component of the human body, and it can contribute to human health and disease. The importance of the interaction *microbes* and *minerals* has been reckoned particularly in the last decades; the so-called

Geomicrobiology became a very interesting field of research. Some microbes are reckoned by their economically useful capabilities, as is the case of the bacterial species of the phyla *Actinobacteria*. It is also known that in certain environments, conditions, and doses, the *minerals* can benefit or affect both the quality of the soil where the animal or vegetable food raises and is produced and the quality of the water and air that the man eats and breathe, respectively.

In the soil and water, minerals can occur in the elemental form which is the bioavailable form and, when in balanced contents, may be essential for sustained and sustainable animal and plant life. For example, it is now widely accepted that the type of soil, which is very much determined by the types of minerals it contains, is a factor that, together with three other factors, caste, climate and winemaking, are essential factors for commercial success, complexity, and originality of a wine, current consumer product. It is the soil that feeds the strains.

Different soils provide different wines even if the grape variety is the same. From this fact the concept of terroir has appeared. Since the 1980s, several studies have emphasized the importance of *rocks'* and *minerals'* quality and quantity in the land where the vine grows. In general terms, granite, shale, limestone, and clay or clay soils decisively influence the final complexity of the wine and its differentiation, which are still influenced by the differentiated varieties of the rocks mentioned above, because there are several granites, shale, limestone, and clays. For example, among clays, there are differences in terms of composition granulometry, mineralogical, chemical and also other properties such as adsorption and water fixation, plasticity, and cation and anion exchange.

If the levels of some bio-essential elements are deficient in the water and in the animal and plant food, the deficiency can be compensated for by the controlled consumption of the so-called mineral supplements for animals (man included) and, for plants deficiency, can be compensated for by the addition to the soil of fertilizers in whose composition the soil chemical elements were deficient.

Mineral water is essential to life, to human body, and to human health. Experience has shown the existence of healing waters, and according to their specific physicochemical properties, they are used in the treatment of specific diseases. The amazing diversity of *mineral waters* used for drinking is definitively due to both the quality and quantity of dissolved minerals, as is clearly shown in the book *Drinking Water Minerals and Mineral Balance: Importance, Health Significance, Safety Precautions* (Rosborg I (editor), 2015, Springer).

Concerning *mineral water*, there is a worrying concern about the increasing exposure of subterranean aquifers, whose mineral water can either be collected for human consumption or perhaps used in *thermalism*. Chemical and microbiological contaminations of anthropogenic origin, although there are aquifers in which, for natural reasons, high concentrations of toxic chemical elements, metals, and/or metalloids occur, make improper the use of water for human consumption. Thermalism is an important economic activity in many countries, including Portugal, with obvious effects on the health and well-being of users. In Portugal, the concepts, objectives, means, and techniques, both fundamental and complementary, of thermalism are established in the so-called Law of the Thermalism, the Decree-Law No. 142/2004 of 11 of June that defines Thermalism as being:

"The use in Thermal Stations or Thermal Centres or yet Thermal spas of natural mineral water (deep circulation water characterized by the stability of its chemical, physicochemical and microbiological properties), and other complementary means for the purpose of prevention, therapy, rehabilitation or well-being."

In the so-called health resort medicine, the use of *thermal mineral waters* for therapeutic purposes is an important component of the *Medical Hydrology*, a scientific field that covers scientific and technical domains dealing with the medicinal use of mineral water (spring water and natural mineral water), methods of application, and solutions.

Thermalism includes *crenotherapy* practices taken place inside the facilities of thermal resorts, or thermal spas, or yet health resort medicine spas, practices that involve the use of certain natural mineral waters or spring waters showing differentiate chemical composition (bicarbonate sodium, gasocarbonic, sulfate calcium, bicarbonate sodium sulfide, chlorinate, etc.), differentiated degree (greater or lesser) of mineralization (hypersaline, mesosaline, and hyposaline), and also differentiate temperature at the emergence site (hot and cold). Such waters of more or less underground deep circulation are considered medicinal products, being used for internal applications (ingestion and inhalation) and/or topical applications (various baths and hydrotherapy), waters that are generally of a more or less deep circulation (Teixeira 2009, 2016).

Crenotherapy may also involve the topical applications of the so-called curative or therapeutic muds and of the so-called cosmetic muds, which are referred to, respectively, as *therapeutic peloids* and *cosmetic peloids* if the natural mud is matured and modified in an artificial environment, and it is recommended to be applied and supervised by medical or cosmetic training professionals.

The therapeutic application of *peloids* is called *pelotherap*y. Inside of the bathhouses, or balnearies, thermal baths, or spas of the thermal resorts, the liquid phase of the mud/peloid being applied is necessarily the *natural mineral water* used in these resorts. The so-called thermal baths, for example, were introduced by the Romans in many European countries; after having passed through a decadence period, they were revived by the Arabs in the case of the Iberian Peninsula.

Thalassotherapy is another interesting economic activity that uses, for therapeutic purposes, naturally occurring highly mineralized seawater or other products from the sea such as mud, salt, sand, algae, and aerosols. In Portugal, for instance, thalassotherapy is practiced in *thalassotherapy centers* (included or not in hotels) and in *thalassotherapy spas* (all hosted in hotels), however still without legal accreditation in what concerns the quality of resources (human and technical) and methods being employed due to the lack of specific legislation. Also, in Portugal, thalassotherapy is practiced in thalasso spa and even in thalassotherapy centers where the use of seawater could be classified as for well-being and not really therapeutics. The *therapeutic thalassotherapy* is distinctive from the *crenotherap*y in terms of the nature of the raw materials being used, the type of pathologies treated, and the methodologies used in the treatments.

Specific legislation deplorably does not exist for the thalassotherapy practiced in Portugal, unlike what happens for the thalassotherapy practiced in France, Tunisia, and Spain. However, specific legislation exists for the crenotherapy practiced in Portugal, ruled by the Decree-Law No. 142/2004, known as the Law of Thermalism.

Minerals *l.s.* can have adverse effects on the human health, effects that in some circumstances can be lethal. Such aggressive effects can be attributed to some minerals *s.s.* or to some natural chemical elements. In the first case, the situation could be represented by *microcrystalline silica*, *asbestos*, and *talc*, present in the air that man needs to breathe, all minerals with origin either natural or anthropogenic (wind-driven dusts, mining works, or ore processing works), eventually causing pathologies called *silicosis*, *asbestosis*, and *talcosis*, respectively; in the second case, some minerals in the elementary form, such as Pb, As, Hg, Sb, Cd, and F, and other elements present in soils, in water (particularly dissolved in underground water), or in air (volcanic gas, industrial gas emissions) can be toxic for man.

Minerals are involved in another process of naturotherapy called *psammotherapy* or *arenotherapy*, yet another economic activity that uses, for the treatment of pathologies of the musculoskeletal forum or simply in wellness practices, baths of the so-called special sands. An example of *psammotherapy* is the case of the traditional biogenic carbonated sand baths that take place in the island of Porto Santo of the archipelago of Madeira, in the natural environment and with the sand exposed to solar radiation, taking care that the sand temperature is not over 41 °C. Natural or artificial heating is essential to produce sweat which, in the interface of human body/sand due to its acid pH, dissolves and turns free Ca, Mg, Sr, and other elements to interact with the body.

At the moment, sand baths also can already take place in bathhouses/balnearies, being the sand heated inside the spa by artificial heating. There are also examples of sand bathing or *psammotherapy* practiced in certain countries, as is the case of places in southern Japan where the sand of volcanic nature is naturally heated by exposure to the volcanic heat, and the case of certain beaches of Guarapari, in Victória do Espirito Santo district, Brazil, where health benefits are assumed to be related to the *radon* emitted from the radioactive monazite-rich sands.

There is an important medical area in which *mineral analogs* or *analogous* play important roles having both positive and negative effects on the human health, such as the so-called biominerals, classified into two groups: bio-essential and pathological. Minerals play equally important and positive roles in the human body through the so-called biomaterials, in the form of metal alloys, special ceramics, and bioactive glasses. It is now possible to manufacture human tissues and organs using the so-called tissue engineering, and stem cells are essential raw materials for this purpose.

The interdependence between pharmacy and therapeutics involving minerals is of course strong, the minerals being the common fundamentals and connecting bridges between two scientific and technical areas which are recognized as so important to health, a reason for the authors of this book to seek to present evidence of this interdependence, both positive and negative. *Minerals* have been used ever since as drugs and in drugs preparation, in accordance with the pharmacopeias, and in which participate *minerals latu sensu* (or *minerals l.s.*), the concept of mineral defined in this same chapter further on. *Geopharmacy*, a secular practice that began with the empirical use and processing of natural substances or drugs of mineral, animal, and plant origin, in modern and contemporary times, has progressively incorporated the growing scientific knowledge that has led to the development of molecular chemistry and the industrial processing of drugs purely synthetic.

In turn *geotherapeutics* is defined as being the scientific domain that within the scope of the Medical Sciences studies prescribes and supervises the use of the *minerals l.s.* for therapeutic purposes. *Geotherapeutics*, which began with the empirical use in antiquity of *minerals*, *metals*, and *clays* (called *medicinal earths* or *medicinal terras*), is a practice which continued until the nineteenth century and was eclipsed in the twentieth century because of the spectacular developments of molecular medicine and the corresponding progress of the pharmaceutical industry. From the foregoing the existence of basic and functional relationships between *geopharmacy* and *geotherapeutics* is clear as expressed through the use of *minerals l.s.*, both in the composition of drugs and in therapeutics, in any of the situations in view of the benefits of the state of human health.

On the *Geological Sciences* side, knowledge about *minerals l.s.* is fundamental, provided in particular by sciences such as mineralogy, geochemistry, and hydrochemistry. On the *Health Sciences* side, the knowledge of *minerals l.s.* is fundamental, in particular for physiology, nutrition, epidemiology, etiology, toxicology, pharmaceutical technology, and clinical medicine. It should be noted that both *geopharmacy* and *geotherapeutics* can be included in the recently emerging scientific field called *Medical Geology*, which targets comprise studies of the properties, benefits, and risks of *minerals l.s.* in *public health*, matters that will be further developed in the following chapters.

Finally, the accomplishment of the broad and specific objectives of this book much had benefited from the complementary contributions of specialists in different scientific fields: geology, chemistry, physics, engineering, medicine, public health, and pharmacy Along the years, experience has shown that in science any great scientific advances require interdisciplinary contributions. Also, along the course of their professional careers, the authors have produced scientific books and articles, most of which related to the subjects dealt with in this book are reported as bibliographical references at the end of the chapters and of some sub-chapters.

References

Balaram V (2019) Rare earth elements: a review of applications, occurrence, exploration, analysis, recycling, and environmental impact. Geosci Front 10(4):1285–1303

Campbell Thompson R (1936) A dictionary of Assyrian chemistry and geology. Clarendon Press, Oxford

Duffin CJ (2013) Lithotherapeutical research sources from Antiquity to the mid-eighteenth century. In: Duffin CJ, Moody RTJ, Gardner-Thorpe C (eds) A history of geology and medicine.

Geological Society of London, Special publication 375, pp 7–43. https://doi.org/10.1144/SP375/25

Duffin CJ (2017) Men, methods and materials: exploring the historical connections between geology and medicine. In: Duffin CJ, Gardner-Thorpe C, Moody RTJ (eds) Geology and medicine: historical connections. Geological Society, London, Special publications, 452. https://doi.org/10.1144/SP452.19

Duffin CJ, Moody RTJ, Gardner-Thorpe C (eds) (2013) A history of geology and medicine. Geological Society of London, Special publication 375. http://sp.lyellcollection.org/content/375/1

Gomes CSF (2003) How Minerals are important for Human Health. In: Ferreira MRP (ed) A Geologia de Engenharia e os Recursos Geológicos. Imprensa da Universidade, Coimbra, pp 379–390

Gomes CSF (2012) Minerais e Peloides no Termalismo. In: Águas Minerais Naturais e de Nascente da Região Centro, (coordenação de Simões Cortez JÁ), Capítulo XIV, 301–379, Mare Liberum (editor), FEDRAVE

Gomes CSF (2013) Naturotherapies Based on Minerals. Geomaterials 3:1–14

Gomes CSF (2015a) In Pelotherapy what is more important, the peloid solid phase or the peloid liquid phase? Balnea 10:125–142

Gomes CSF (2015b) Semelhança, Dissemelhança e Interdependência entre o ser humano e o ser mineral. O Liberal Comunicação Lda (editor), Câmara de Lobos, RAM, 369pp. ISBN: 978-989-8503-73-2

Gomes CSF (2017) Notas sobre Água, Terra, Vida e Saúde. In: Águas Minerais Naturais e de nascente da Região Norte, (coordenação de Simões Cortez JÁ), Capítulo VIII, 285–352, Mare Liberum (editor), FEDRAVE

Gomes CSF, Silva JBP (2003) Potencialidades das Areias Carbonatadas Biogénicas do Porto Santo para Aplicações em Geomedicina. In: Ferreira MRP (ed) A Geologia de Engenharia e os Recursos Geológicos. Imprensa da Universidade, Coimbra, pp 367–378

Gomes CSF, Silva JBP (2006) "Minerals and human health: benefits and risks" / "Os Minerais e a Saúde Humana: Benefícios e Riscos". Multiponto, 4000–299 Porto, 142 pp/158 pp

Gomes CSF, Silva JBP (2007) Minerals and clay minerals in medical geology. Appl Clay Sci 36:4–21

Gomes CSF, Silva JBP (2010a) Impactes Positivos de Minerais e Ambientes Geológicos na Saúde Humana. In: Publicação Comemorativa do Ano Internacional do Planeta Terra. Associação Portuguesa de Geólogos e Sociedade Geológica de Portugal (editores), vol. II – Geologia Aplicada, Geologia e Ambiente, pp 229–238

Gomes CSF, Silva JBP (2010b) Impactes Negativos de Minerais e Ambientes Geológicos na Saúde Humana. In: Publicação Comemorativa do Ano Internacional do Planeta Terra. Associação Portuguesa de Geólogos e Sociedade Geológica de Portugal (editores), vol. II – Geologia Aplicada, Geologia e Ambiente, pp 219–228

Gomes CSF, Silva JBP (2012) "Ilha do Porto Santo: Estância Singular de Saúde Natural" / "Porto Santo Island: Unique Natural Health Resort". Madeira Rochas-Divulgações Científicas e Culturais (editor), Funchal, RAM, 239 pp

Hall AJ, Photos-Jones E (2008) Assessing past beliefs and practices: the case of Lemnian earth. Archaeometry 50(6):1034–1049

Hoch E (2017) Earth Science as a Philosophical Back-ground to Medicine: an essay based on the autobiography of Dr. Otto Sperling (1602–81) In: Duffin CJ, Gardner-Thorpe C, Moody RTJ (eds) Geology and medicine: historical connections. Geological Society of London, Special publication 452. https://doi.org/10.1144/SP452.18

Kalantzabos S (2019) The Geopolitics of Critical Minerals. IAI Papers 19/27 Dec 2019, 15pp, Instituto Affari Internazionali. ISBN 978-88-9368-119-3

Kogel JE, Trivedi NC (2006) In: Barker JM, Krukowski ST (eds) Industrial minerals & rocks: commodities, markets and uses, 7th edn. Society for Mining, Metallurgy, and Exploration, Inc, Littleton

Lam PL, Lee KKH, Wong RSM, Cheng GYM, Bian ZX, Chui CH, Gambari R (2018) Recent advances on topical antimicrobials for skin and soft tissue infections and their safety concerns. Crit Rev Microbiol 44:40–78

Macgregor A (2013) Medicinal terra sigillata: a historical, geographical and typological review. Geological Society, London, Special publication 375, pp 113–136

Photos-Jones E, Edwards C, Haner F, Lawton L, Keane C, Leanord A, Perdikatsis V (2017) Archaeological medicinal earths as antibacterial agents: the case of the Basel Lemnian sphragides. In: Duffin CJ, Gardner-Thorpe C, Moody, RTJ (eds) Geology and medicine: historical connections. Geological Society, London, Special publication 452. https://doi.org/10.1144/SP452.6

Rautureau M, Gomes CSF, Liewig N, Katouzian-Safadi M (2010) Argiles et Santé : Propriétés et Thérapies. Édition Médicales Internationale, Lavoisier, 184pp

Rautureau M, Gomes CSF, Liewig N, Katouzian-Safadi M (2017) Clays and health: properties and therapeutic uses. Springer, Cham. ISBN 978-3-319-42883-3

Retsas S (2016) Geotherapeutics: the medicinal use of earths, minerals and metals from antiquity to the twenty first century. In: Duffin CJ, Gardner-Thorpe C, Moody RTJ (eds) Geology and medicine: hstorical connections. Geological Society, London, Special publications 452 452. https://doi.org/10.1144/SP452.5

Teixeira F (2009) Água, Fonte da Vida. In: Comissão de Coordenação e Desenvolvimento da Região Centro (ed) À Beira da Água, pp 109–139. ISBN: 978-972-569-160-1

Teixeira F (2016) Termalismo terapêutico em Portugal: Presente e Perspectivas Futuras. Revista Factores de Risco, Sociedade Portuguesa de Cardiologia 41:26–37

USGS (2014) Science for a changing world: the rare-earth elements vital to modern technologies and lifestyles. Fact Sheet 2014–3078, Nov 2014

Viseras C, Carazo E, Borrego-Sánchez A, Garcia-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C (2019) Clay minerals in skin drug delivery. Clays and Clay Minerals, published online 05 April. https://doi.org/10.1007/s42860-018-0003-7

Chapter 2
Minerals, Natural Environment, and Medical Geology

Celso S. F. Gomes

Abstract The increasing concern of modern societies with the interactions between the environment and human health, in particular through the geological processes and products, justified the emergence in the last two decades of the scientific field called Medical Geology, which has been mainly focused on the negative or hazardous effects of minerals. The scientific field of Medical Geology is strongly interdisciplinary and is a matter of interest and involvement of people with professional education and training in diverse scientific areas, such as medicine, geology, biology, biochemistry, biophysics, mineralogy, geochemistry, hydrogeology, hydrochemistry, ecology, environment, food chemistry, pharmacy, nutrition, toxicology, pathology, epidemiology, etiology, territory planning, and economics. For instance, minerals could participate in the formulations of pharmaceuticals and cosmetics as active substances and as excipients, and could participate in mineral supplement formulations too. Minerals in the so-called elemental form are essential constituents of mineral water used for human consumption and are also used in naturotherapies involving mineral water such as mud therapy/pelotherapy, balneotherapy, crenotherapy, and thalassotherapy, mostly taking place in thermal spas where health resort medicine is practiced under medical counseling and supervision. Also, minerals in the elemental form and as minerals *stricto sensu* can cause pathologies that, in specific circumstances, can be lethal.

2.1 Minerals and the Natural Environment

As already mentioned in Chap. 1, *minerals* are present throughout the *natural environment*, as constituents of rocks, sediments and soils; in suspension and/or solution in the waters of both surface and underground aquifers; as constituents of the living beings (animals and plants) regardless of their hierarchy; and also suspended in the

---

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_2

air. And minerals are also present in the built environment, for instance, as constituents of the raw materials used in the construction of dwellings and of other urban and rural equipment, in industrial and agricultural machinery, and in communication and other means. The natural environment where the man is created and uses it for its own survival and pleasure are two very complex entities that enter several components and variables that have not yet been fully identified and whose interaction is also far from being satisfactorily understood.

Presently we are passing through a environmental crisis worldwide discussed and called -climatic changes- with great impacts, for instance, on biodiversity and water use, and man unquestionably contributes much for it, since the so-called Industrial Revolution, becoming every time more accentuated as far as humans seeking improvement of living quality and ersona require the use of more and more energy, what is being achieved from the increasing exploration and exploitation of mineral resources.

Man has capacities to change landscapes, river courses, agriculture soils, biological resources, etc. As a matter of fact, industrialization rapidly has contributed to climatic changes, and consequently man has been an agent of inexorable long-lasting changes in the natural systems, almost impossible to recover, that surely will affect himself, particularly his health, hoping that scientists can play a paramount role providing the politicians with facts and solutions.

Man's current increasing concern of negative impacts on the environment is well expressed by Pope Francis in his second Encyclical Letter entitled *Laudato si*, meaning in English "Praise be to You", and subtitled *On Care for Our Common Home*, originally published in June 18, 2015, enhances the paramount importance of the *ecology*.

The word *ecology* derives from the Greek word "oikos" meaning "house" and is defined as the "branch of Biology dealing with the relationships among organisms, humans included, and their environments." The word *ecology* was coined in 1866 by the German scientist Ernst Haeckel. The Ancient Greek philosophers Hippocrates and Aristotle really laid the foundations of *ecology* in their studies on natural history.

Chemical elements and minerals themselves hereinafter defined, rocks, soils, water, and air, are the essential foundations or components of the natural environment where man has his habitat and interacts with him. Over time, man has acquired experience about the existence of interactions between the mentioned components (Fig. 2.1), as well as about the beneficial and deleterious effects that the natural and constructed environment has on living beings, man, other animals, and plants.

Environmental factors affect human health, and their effects may be both positive and negative (WHO).

Positive environmental factors support health, and its promotion corresponds to the so-called preventive medicine. These factors include the following:

1. Nutrition sources: agriculture (soil quality, water availability), livestock, and fisheries.
2. Water quality (water for drinking and water for cooking).
3. Air quality.

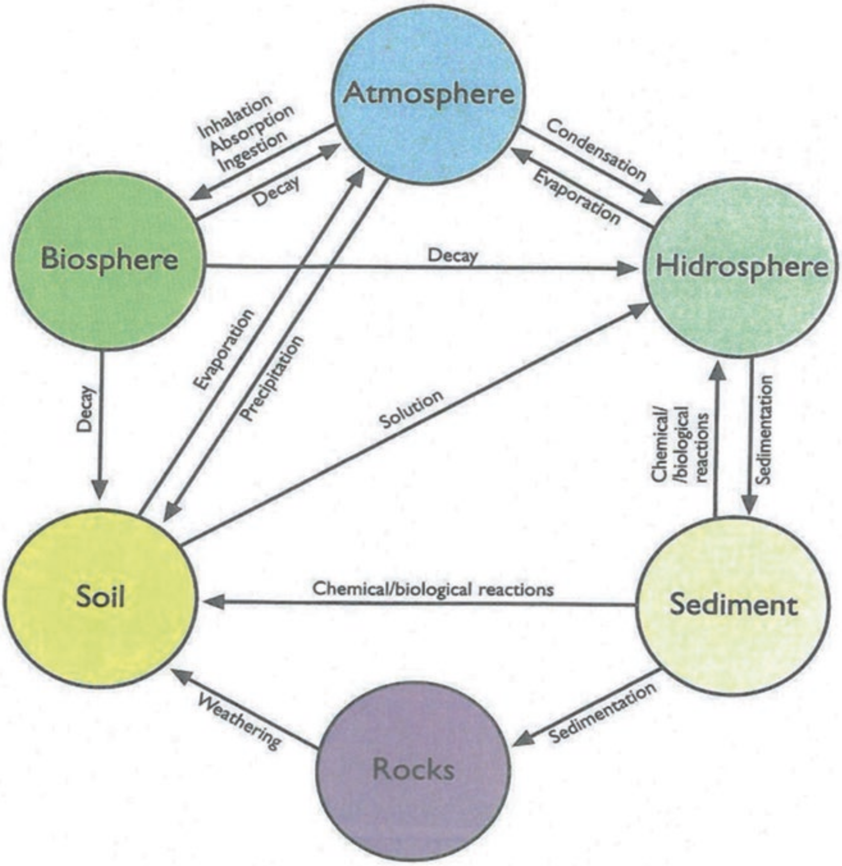


Fig. 2.1 Relationships of interdependence between rocks, soils, sediments, hydrosphere, biosphere, and atmosphere that occur in the natural environment, with potential and real reflections on the health of man and of other animals

4. Ozone layer (protection against UV radiation); ozone pollution in the atmosphere influences the number of ultraviolet B (290–315 nm) photons of the sun's radiation that reaches the Earth's surface and therefore alter the cutaneous production of cholecalciferol (vitamin D) essential for the maintenance of skeletal calcification (Holick 1995).
5. Sanitary measures (recycling, deposition, and treatment of solid waste and deposition and treatment of waste water).

Negative environmental factors constitute health risks, and their control is called *public health*. These factors include the following:

1. Environmental conditions favoring disease vectors (endemic vectors and exogenous vectors).

2. Invasive biota (viruses, bacteria, etc. and their hosts and vectors).
3. Environmental disruptions (floods, droughts, storms, fires, earthquakes, volcanoes, and landslides).
4. Water quality (biotic and abiotic contaminants).
5. Air quality (pollution causing respiratory diseases and carcinogenic affections).
6. Monitoring and management of municipal, agricultural, and industrial effluents (gases, liquids, and solid wastes).
7. Changes in the natural environment, due to human activity, which create conditions that favor the onset and development of diseases, destabilize, and release harmful levels of potentially toxic chemical elements that were previously part of stable compounds (e.g., Hg, As, Pb, Cd, Sb, and Ba) in the form of sulfides, arsenides, and sulfates, etc.) or biota (e.g., methane released from peat defrost).
8. Humanity is subject to large-scale threats, whether natural or man-made. In the latter case, the following are highlighted: severe climate change, chemical weapons, bacteriological weapons, and nuclear weapons.

The minerals *l.s.* have a great influence on human health because they can positively and negatively influence soil, water, and air quality and condition the diversity and quality of the *ecosystems*. Minerals are the fundamentals of the other natural resources, particularly conditioned by the fact that soil and water are limited resources, and so they determine the "global ecologic footprint." The living resources could be regenerated, while the mineral resources could not. The relationships and interdependencies between living organisms, microorganisms included, and minerals *l.s.* are becoming more and more well known, a situation that led to the appearance of two new disciplines called *biogeochemistry* and *geomicrobiology*.

To promote cell growth and support metabolic activity, all microorganisms need metals such as magnesium (Mg), sodium (Na), potassium (K), iron (Fe), copper (Cu), molybdenum (Mo), nickel (Ni), zinc (Zn), chromium (Cr), and manganese (Mn), which they extract from *minerals themselves* or *minerals s.s.* existing in rocks, soils, and waters. Also, metals such as iron (Fe), arsenic (As), magnesium (Mg), uranium (U), selenium (Se), and vanadium (V) are used as energy sources by microorganisms. Otherwise the microorganisms interact with the minerals *l.s.* subjecting them, so many times, to oxidation-reduction reactions which, through solubility, mobility, and precipitation, can redistribute metals in the Earth's crust and, consequently, enrich or concentrate certain metals in certain places, and their economic interest could justify studies and projects regarding the feasibility of exploitation.

It is unquestionable that both the information empirically acquired since the antiquity and the scientific information that has been acquired since then show that the concept or definition of *mineral l.s.* encompasses the minerals themselves or *minerals s.s.*, defined as natural, inorganic, and crystalline solids, and the chemical elements, defined as natural and inorganic in origin, which either form the *minerals themselves* or occur in them in an accessory and minor manner.

The chemical elements also occur in the environment, either in the free form in ionic solution, or dispersed in the atmosphere, or yet in soil reversibly affixed to the external surfaces of the secondary or supergenic minerals, such as clay minerals, which may both be essential and beneficial to the life of humans, animals, and plants and deleterious to these same beings when in excess or in deficiency.

The *minerals s.s.* are constituted of natural chemical elements, either of a single essential element (in the case of minerals called *native elements*) exemplified by *copper* (Cu), *gold* (Au), and *silver* (Ag), or by associations in a parsimonious number of different elements in the ionic form (cations and anions), whose classification or systematics (oxides, hydroxides, sulfides, sulfates, carbonates, silicates, etc.) is determined by the nature of the anion. The processes of *minerals s.s.* formation, i.e., of *mineralogenesis*, are the same that lead to the formation of crystals (crystalline solids, characterized by internally ordered organizations or three-dimensional and tri-periodic structures), that is to say of *crystallogenesis*, processes that are limited to four possibilities, as follows:

1. Solution → crystal (precipitation);
2. Vapor → crystal (sublimation);
3. Melt → crystal (freezing);
4. Crystal A → crystal B (transformation).

To concretize these four possibilities, it is required that the *free energy* of the crystal being formed is less than the *free energy* of the producing system.

Mineralogy is the science of minerals and has close relationships with other sciences as well as strong actual and future impacts on the environment, and consequently on the systems that support life on Earth: soil, water, atmosphere, and biosystems. Diversity is a general and common characteristic within the various species of *minerals s.s.*, the reason why the concept of *individual mineral* has been established. The environment is the major epigenetic factor contributing to the individual mineral diversity. The same happens within the human species; diversity can even happen within homozygous twins (born from the same egg), time, environment, and diet being the epigenetic factors responsible for both individual phenotype and genetic differentiation.

According to Hochella (2002), minerals provide a fundamental contribution to a sustainable Earth in the following three reasons:

1. Minerals interact dynamically with the natural waters on the surface of the Earth where low temperatures and low pressures prevail, the final products being the generation of soils and groundwater with differentiated characteristics.
2. Minerals interact with the atmosphere significantly affecting atmospheric chemistry and rapid transport, potentially over long distances, of inorganic and organic substances; minerals in the atmosphere, soil and groundwater can promote a vast number of diseases.
3. Minerals have always represented and continue to represent a significant portion of resources whose extraction from the Earth is necessary for the development and modernity of civilizations; yet the mining and processing of mineral resources (oil and coal included) contribute devastatingly to the pollution and destruction of the planet.

The *mineral s.s./water* interaction is complex depending on the nature of the mineral and on its estimated solubility through hydrochemistry and "sorption"/"desorption" processes.

The constituent chemical elements of minerals, most of them classified as metals, become free forms, with greater or lesser reactivity in the case of metals that may have deleterious consequences on the human health depending on the ionic forms or species in which they occur. In order to predict, mitigate, and remediate the potential health effects of metals in the environment, it is crucial to understand:

1. The geological, mineralogical, and chemical occurrences of metals in earth materials;
2. The geochemical and biochemical processes that control metal mobility in the environment.

In the case of metals, the chemical form and concentration in the environment strongly influence their uptake by and toxicity to plants and organisms. In order to be bioavailable, a certain metal existing in an earth material, it must first be *geoavailable*.

Sustainable Earth means maintaining the functional systems that support life on the planet and avoiding its long-term decline, so that human habitation on the planet is unlimited. The minerals *l.s.* can have both positive effects and negative effects on human health, effects disclosed in several chapters of this book.

Among the chemical elements it is also enhanced the participation of metals in the composition of organometallic complexes, in the case of proteins with special emphasis on enzymes (in which the so-called transition metals or heavy metals have particularly relevant functions), which are essential for the vital functioning; also, chemical elements that can be part of salts, the so-called mineral salts, are common in nutritional supplements.

As much as the so-called minerals themselves or minerals *s.s.*, natural chemical elements, which in this book are considered minerals, may participate, either as active substances or ingredients, or as excipients in pharmaceuticals, and also as trace elements into the formulations of *nutritional supplements*. But the concept of *mineral l.s.* adopted in this book is even more comprehensive than previously mentioned, encompassing, for example:

1. Certain types of natural and coherent assemblages of minerals, exemplified by special clays such as *kaolin*, *bentonite*, and fibrous clays (*sepiolite* and *palygorskite*), which after being refined and beneficiated to a greater or lesser degree can participate in drug formulations as active substances or as excipients.
2. Certain types of *natural mud* to which curative properties are recognized, as well as certain types of mud which has been manipulated and maturated, that are artificialized in some way are called *peloids* to which medically recognized curative properties are attributed.
3. Certain types of mineral water (*seawater*, *salt-lake water*, *spring water*, and *natural mineral water*), all mineral resources in which certain minerals are recognized as well as certain chemical elements that determine their health benefits.

4. The so-called biominerals, which are *analogs* of *minerals s.s.*, are developed naturally inside the human body forming, for instance, the bones, teeth, kidney, and bile stones and other mineralizations; and also the so-called synthetic minerals industrially produced based on the elements or compounds derived from minerals such as certain varieties of oxides, phosphates, and carbonates and the synthetic clay mineral called *laponite*, $Na_{0.7}Si_8Mg_{5.5}Li_{0.3}O_{20}(OH)_2$, an important rheological modifier of certain pharmaceutical formulations.

It is well known that minerals *l.s.* participate in the constitution of all living beings, and condition the quality of the natural systems that are life support: *soil*, *water*, and *atmosphere*.

In humans, minerals play three main beneficial roles:

1. Provide structuring in the formation of the bones and teeth
2. Help in the maintenance of normal heart rate, muscle contraction and conduction of the nervous system, and acid/base balance
3. Regulate cellular metabolism by being part of enzymes and hormones that control cellular activity

Minerals can also have deleterious effects on humans. It is known that a good part of the human diseases is related to minerals of either *geogenic* or *anthropogenic* origin present in the natural environment that serves as habitat for the man. It is also known that some diseases are related to lifestyle; others are due to the action of pathogens (viruses and bacteria), and several others are genetically dependent.

Effectively it is demonstrated that in the natural environment man's exposure to certain geological materials and processes can be a cause of disease, some of which can be lethal, for example, excessive exposure to certain potentially toxic chemicals, such as arsenic, lead, cadmium, mercury, selenium, fluorine, uranium, and radon, which may be present, either in the soil particularly affixed to the surfaces of clay minerals and utilized by plants which are at the base of the food chain, or in the water, or yet in the air. The knowledge of the connection is remote, sometimes with catastrophic effects, between the geological phenomena and the life and health of man. Physical manifestations of this connection with devastating effects on human life are highlighted by natural disasters caused, for instance, by volcanic eruptions, earthquakes, landslides, windstorms, hurricanes, tornadoes, wildfires, severe floods, and tsunamis, as well as by human-caused disasters, for instance, urban fires, armed conflicts, and industrial spills. Such disasters pose acute threats to human health and safety as well as for the long-lasting impacts from physical injuries and effects on chronic diseases and mental health (Landesman 2006; Hogan and Burnstein 2007; Miller and Arquilla 2008; Mason et al. 2010).

The disasters can produce too substantial physical and chemical stresses and impacts on the environment with consequences on ecosystems and humans. Plumlee (2009) and Plumlee et al. (2012) (in the context of urban disasters) have reported examples of environmental and health implications caused by the hazardous materials (HM) or disaster materials (DM), such as volcanic ash, volcanic gas, volcanic mud, mine wastes and tailings, acid mine drainage, debris flow, muddy flood, dust plumes, and smoke plumes, after being released into the environment by various natural and man-caused disasters, and the toxicological characteristics of those HM or DM. Plumlee et al. (2014) illustrate the important roles that geochemists and other earth scientists can play in understanding DM, and therefore in assisting in environmental disaster responses.

The knowledge of the relationship between the natural environment and health is also remote, the disease being the result of exposure to the natural environment, a situation recognized by Hippocrates (ca. 460–370 B.C.), a Greek physician who was considered the "father of Medicine," and discussed in Chaps. 3 and 4 of this book.

2.2 Minerals and Medical Geology

The recognition of the existence of direct relations between geology, represented essentially by mineralogy and geochemistry, and human/animal health has recently provided the development of a new scientific area called Medical Geology (Bowman et al. 2003; Jaramillo-Nieves and Finkelman 2012). These relationships date back to the antiquity (Duffin et al. 2013).

Medical Geology can be defined in the broad sense as the scientific field that studies the interaction of the environment with health. Effectively the object of Medical Geology is the study of the positive and negative effects of minerals *l.s.*, geogenic and anthropogenic, on public health.

The first steps for the creation of an international network in Medical Geology started in 1996 in Uppsala, Sweden. The Medical Geology designation was proposed in 1996 by the Committee on Geological Sciences for Environmental Planning (COGEOENVIRONMENT) of the International Association of Geological Sciences (IUGS), which established a working group on Medical Geology with the mission of alerting specialists in Geosciences and geology, medical experts, and the general public to the importance of the impacts of geological factors on the health and well-being of billions of people around the world. In 1997, at a meeting of the aforementioned working group held in Vale, Colorado, USA, the designation *Medical Geology* was approved and adopted.

It looks like that the first reference to the term *Medical Geology* is found in a scientific article entitled "Medical Geology and Geography" produced by Warren (1965).

Prior to the adoption of the designation *Medical Geology*, many of the objectives of this broad and interdisciplinary scientific field were contemplated under other names.

In the 1930s of the twentieth century, terms "Geomedicine/Geographical Medicine" corresponded to the "Science that used geographic and cartographic methods to explain the results of medical research." In 1990, in Norway, the designation "Geomedicine/Geographical Medicine" was redefined as "The science that deals with the influence of environmental factors on the geographic distribution of the disease" (Låg 1990).

In turn, the term "Medical Geology/Geochemistry" means the studies of "The effects of geochemical processes and geological factors on the health of humans and plants." Also, it is commonly accepted that a person's health depends on where he or she lives, as well as the place or places where he or she lived in the past and how long he or she lived in those places (Davenhall 2009, 2010, 2012, 2014).

Dissanayake and Chandrajith (2009a, b) in the book titled *Introduction to Medical Geology: Focus on Tropical Environments* show various cases of diseases, such as *podoconiosis* and *Kaposi's sarcoma* (KS) that mostly occur on tropical environments, in Africa in particular, environments which are characterized by particular climate, geology, soil formation (temperature and water accelerate mineral weathering), and consequent soil deficiency and enrichment in certain trace elements, essential or toxic to humans.

According to Ziegler (1993), *podoconiosis* and *KS* are excellent examples of diseases which clearly illustrate the interrelationship between geology and health in tropical areas where the pathways of chemical elements and minerals from the immediate environment to the body is direct. *Podoconiosis* is prevalent in areas with fine reddish-brown soils derived from alkali basalt rocks weathering. KS is believed to arise in the lymphatic endothelium and is associated with chronic lymphedema, and in Africa, is related to the regions of ultrabasic basalt provinces and the prevalence of podoconiosis.

The term "geochemical diseases" is attributable to such cases where the etiology of a certain disease is almost directly and clearly related to a characteristic elemental composition of the immediate geological environment. Very recently Korobova et al. (2020) produced an interesting paper entitled "Endemic diseases of geochemical origin and methodological approaches toward their prevention and elimination." Two genetically different types of endemic diseases of geochemical origin are distinguished, each having a specifically spatial structure:

1. Diseases of natural origin due to natural element deficiency or excess in the particular zones or areas;
2. Diseases of anthropogenic origin related to chemical transformation of the environment in the course of agricultural or industrial production.

The last type referred to is exemplified with a modern endemic disease expressed by the increasing number of people affected by thyroid cancer caused by the fallout of radioactive iodine isotope ^{131}I and consequent soil contamination observed after the Chernobyl nuclear accident which occurred in 1986, in the Republic of Belarus and western Russia.

Plumlee et al. (2014) report the aspects of the emerging discipline "Medical Geochemistry," specifically the application of geochemical principles and methods to understand the interactions between body fluids and earth materials and how these interactions may influence toxicity, a discipline that can also be appropriately termed "toxicological geochemistry" (Plumlee et al. 2006).

Jaramillo-Nieves and Finkelman (2012) consider that Medical Geology and environmental geochemistry are closely related disciplines. In general, environmental geochemistry is a prospective science characterizing the chemical elements in a region and identifying potential environmental consequences of elemental anomalies. Medical Geology is more of a retrospective science generally starting with known health issues and trying to determine the geologic causes. The disciplines merge when the environmental geochemical anomalies result or may result in the health problem of animals or people in the region.

According to Boulos and Le Blond (2016), the geographical history of patients should be taken into account by physicians in the diagnosis and treatment of the disease. Research on Medical Geology in the search for relationships between the environment and human health should involve a large number of areas of knowledge and specialists. Effectively the diagnosis, prevention, and personalized treatment of a disease related to geology can only be achieved through a wide interdisciplinary collaboration.

In 2006, the International Medical Geology Association (IMGA) was established, presently with about 500 members from all around the world gathered in national groups (http://www.medicalgeology.org).

In Medical Geology in addition to the *minerals themselves* or *minerals stricto sensu*, most chemical elements (metals and metalloids) present in mineral spring waters, whether thermal or not, are also considered minerals, and also in other types of surface or underground water used for human consumption, the chemical elements, metals, and metalloids present in natural gas emissions (volcanic emissions) and the gas *radon* emitted in areas where radioactive ores are present are also considered as minerals. Both *metals* and *metalloids* of anthropogenic origin that makes up the gaseous emissions derived from industrial activities, such as ceramics and cement, with emissions of mercury, fluorine, and sulfur, are also of interest in Medical Geology.

Bunnell (2004) following a conference meeting held in Washington, D.C., in June 2002, of the working group on "Medical Geology: Earth Systems, Resource Use and Human Health," and in the context of the conference under the theme "Healthy Ecosystems/Healthy People," makes some interesting considerations about the conclusions of the meeting and about the definition of Medical Geology. Bunnell says that Medical Geology is "An emerging discipline that broadly examines the impacts of geological materials and processes on human health and ecosystems." This concept would include both natural sources and potential anthropogenic sources of health problems, not only of man but also of wildlife and plants.

Bunnell (2004) states that "In contrast to the emphasis on treatment and cure of disease, the word Medical in the term Medical Geology implies that the subject of the discipline could be more accurately described as Public Health because of its focus on disease prevention, and even though the term Medical Geology is not perfect to describe the discipline, it has the advantage of being simple to use and remember and still be accessible both to policy makers and the public." Also, according to the same author, the term that would best describe the discipline would be hydrobiogeochemicoepidemiopatholoecology, but whose use does not make sense for obvious reasons. For Bunnell (2004), the objectives and scope of Medical Geology would be the following:

1. Identify and characterize the natural and anthropogenic sources of harmful materials existing in the environment;
2. Learn how to make predictions about the movement and alteration of chemical, infectious, and other disease-causing agents in time and space;
3. Understand the reasons why people are exposed to such materials and what can be done to prevent or minimize the effects

Most Medical Geology research has been focused on health problems caused by excess or deficiency of chemical elements, particularly of trace elements.

Finkelman (2006) report examples of health benefits of geologic materials and geologic processes, in particular of clay, clay minerals, and other minerals used today in a wide variety of pharmaceuticals and healthcare products. The same author, Finkelman (2007), report examples of health risks provided by geologic materials, exemplified by trace elements released from coal use in Guizhou province, southwest of China, where millions of people suffer from dental and skeletal fluorosis and thousands suffer from arsenic poisoning due to mobilization of these elements by burning mineralized coals in unvented or poorly vented stoves.

Gomes and Silva (2007), commenting on the correctness of the term *Medical Geology*, consider that the term *geology* corresponds to "A scientific area with objectives not limited to the study of chemical elements and minerals that apparently are the essential factors that intervene or are conditioners of human/animal health." These same authors also consider that the term *medicine* corresponds to "A scientific area with objectives that are not limited to the simple identification and interpretation of the impacts of chemical elements and minerals on human and animal health." Indeed, *geology* is the science that deals with the study of the Earth using methods of other sciences and methods proper to geology in order to investigate the nature, processes, and history of the Earth. And, according to Gomes and Silva (2007), medicine relies on three basic interdependent pillars: *scientific information*, *diagnosis*, and *therapeutics*. It is in the field of *scientific information* that geology can be useful to public health.

The main objective of the studies in the field of Medical Geology is to identify the cause of the disease: first, to allow the desired medical intervention and, second, to be able to prevent the disease. Boulos and Le Blond (2016) considered that the beginning of an investigation in Medical Geology can follow one of two fundamental methodologies:

1. Identification of the disease in individuals or in populations
2. Recognition of the presence of the contaminating substance (chemical element or compound) in the environment, a potential cause of health disorders

Also, according to Boulos and Le Blond (2016), the prognosis, the prevention of the disease, and, if possible, a personalized treatment can only be achieved through multidisciplinary, interdisciplinary, and transdisciplinary interventions.

Andrews et al. (2004) differentiate the concepts of *contaminant* and *pollutant*. The term *contaminant* is applied to the substance, element, or "ground level." In turn, the term *pollutant* is applied to the compound which is present in the environment in a concentration higher than the "natural background" when the pollutant is assigned a deleterious effect on the environment, particularly in humans that may be present in it.

On the other hand, the intimate relationship between *minerals* and *human/animal health* cannot be limited to the adverse or negative effects of certain chemical elements, in particular certain *heavy metals* and *metalloids*, of both geogenic and anthropogenic origin, or of certain minerals existing in the environment. Anyway, independently of the meaning of the term Medical Geology, this is an emerging and very interesting scientific area that should cover not only the negative effects but also the positive effects of mineral resources or *minerals l.s.* on human/animal health. It should be noted that it is the negative effects of *minerals l.s.* which deserve the almost exclusive attention of scientific meetings, scientific journals, and the media.

Medical Geology evaluates the complex relationships between geoenvironmental factors and their impacts on humans and, in its integrated way, promises a more holistic understanding of the occurrence, mobility, bioavailability, bio-accessibility, exposure, and mechanisms of transfer of contaminants of geogenic origin in the food chain and human health, as well as ecotoxicological impacts and health effects and identification of the etiology of the disease caused.

The book entitled *Essentials of Medical Geology: Impacts of the Natural Environment on the Public Health* edited by Selinus et al. (2005) is a reference text that emphasizes the role of the natural environment, measured essentially by the interaction of the chemical elements (oligoelements or trace elements, or trace minerals, or yet micronutrients) with the human body and, mainly, shows the negative effects on human health from its influx and incorporation. The same editors, in 2013, have issued a second edition of this book. In the following year, 2006, the "Geochemical Society" and the "Mineralogical Society" of the USA jointly published another book entitled *Medical Mineralogy and Geochemistry* edited by Sahai N and Schoonen AA.

The above referred to interactions between natural environment and human health, which are objectively the target of a recent research field called *environmental geochemistry,* well represented by the book entitled *Concepts and Applications in Environmental Geochemistry*, published in 2007, Sarkar D, Datta R, and Hannigan R being the editors.

Geochemists prefer the designation *Medical Geochemistry* or even the designation *Toxicological Geochemistry* to the designation *Medical Geology*. Plumlee and Ziegler (2007) and Plumlee et al. (2014) used both terms referred to in a chapter dedicated to Environmental Geochemistry included into a book entitled *Treatise on Geochemistry*, first edition and second edition respectively: the authors using geochemical principles and methods emphasize the adverse health effects of dusts, soils and other earth materials and potentially hazardous materials produced by natural disasters such as: volcanic eruptions, volcanic gases, volcanic ashes, landslides and debris flows, hurricanes, floods, wildfires, and mine wastes and mill tailing impoundment failures.

Finkelman et al. (2018) were the authors of a chapter entitled “Applications of Geochemistry to Medical Geology” of the book *Environmental Geochemistry*, second ed., published by Elsevier, in which the authors provide examples of how the discipline of geochemistry provides insights into and how the natural environment impacts animal and human health. The authors enhance how geochemical maps can help identify regions where soil, rocks, and water have elevated levels of harmful elements or where soils are depleted in essential elements. In 2005, the *Geochemical Atlas of Europe* was published by Salminen et al. (2005). It was the result of a coordinated program carried out by the government institutions from 26 countries under the auspices of the Forum of European Geological Surveys (FOREGS). The main objectives of this European survey were:

1. To apply standardized methods of sampling, chemical analysis, and data management to prepare a geochemical baseline across Europe;
2. To use this reference network to coordinate national baseline datasets.

Altogether, 360 geochemical maps showing the distribution of more than 50 chemical elements across Europe were prepared. All the results and field observations were organized in a common database and the maps published in the *Geochemical Atlas of Europe* (http://weppi.gtk.fi/publ/foregsatlas/). In many countries around the world, mapping projects like these have been developed.

Medical Geology was included as one of the ten main themes of the International Year of Planet Earth under the title “Earth and Health – for a Safer Environment.” Under the coordination of IUGS and UNESCO, in 2010, the International Year of Planet Earth was conceived to show the general public how earth sciences are contributing to society’s well-being by making the world safer and healthier.

The worldwide increasing interest for Medical Geology justified the issue, in 2010, still of another book entitled *Medical Geology: A Regional Synthesis* having as editors Selinus O, Finkelman RB, and Centeno JA, book that discloses several examples of the essentially negative effects of the interaction of the both geological environment and geological resources on human and animal health already identified in regions, such as North America, Central America, South America, Australia and Oceanie, Africa, Middle East, India and neighboring regions, Europe, Russia, China, Japan, and Hellas (Greece). Figueiredo et al. (2010) report interesting studies on Medical Geology carried out in South America.

The books referred to have opened doors to research lines on topics related to the interaction between the environment and human/animal health that require further experimentation, discussion, and confirmation. It will be important to find the best strategies to provide viability and visibility to a scientific domain so important to the public health. Also, examples of the natural environment / health interaction are provided in various relatively recent publications, such as. Bunnell et al. (2007), Chamley (2003), Davies (2010), Dissanoyake & Chandrajith (2006), Finkelman et al. (2001), Gomes & Silva (2006), Keller (2002), Komantina (2004), Sahai & Schoonen (2006), Sahai et al. (2006), Selinus (2004), Selinus et al. (2013), Selinus et al. (2010), Silva et al. (2010), Skinner (2000), Skinner & Berger (2003), Skinner (2005), Zheng et al. (2010), Boules and Blond (2016), Buck et al. (2016), Centeno et al. (2016), and Finkelman (2019).

Environmental Health has been defined by the World Health Organization (WHO) in a 1999 document as: "Those aspects of the human health and disease that are determined by factors in the environment. It also refers to the theory and practice of assessing and controlling factors in the environment that can potentially affect health."

Environmental health, a concept more comprehensive than the concept of *Medical Geology*, is defined as the branch of public health that is concerned with all aspects of the natural and built environment that may affect human health. *Environmental health* is the science, practice, and study of a human's well-being and their health and preventing illnesses and human injuries. *The environmental health* concept as used by the WHO Regional Office for Europe includes both the direct pathological effects of chemicals, radiation, and some biological agents and the effects, often indirect, on health and well-being of the broad physical, psychological, social, and cultural environment, which include housing, urban development, land use, and transport. Other terms referring to or concerning *environmental health* are *environmental public health* and *public health protection/environmental health protection*.

Environmental health and *environmental protection* are very much related. *Environmental health* is focused on the natural and built environments for the benefit of human health, whereas *environmental protection* is concerned with protecting the natural environment for the benefit of human health and the ecosystem. Research in the *environmental health* field tries to limit the harmful exposures through natural things such as soil, water, air, food, etc. Regarding soils, they form an integral link in the holistic view of human health, and some have recognized that there are connections between soil and human health going back thousands of years (Brevik and Burgess 2013).

Brevik and Sauer (2015) produced an interesting paper entitled "The past, present, and future of soils and human health studies." The authors state that soils have distinct influence on human health since they condition food availability and quality (food security), human contact with various chemicals, and human contact with various pathogens. The paper is an excellent review of the existing links between soils and human health, and offers some opinions regarding future needs in soils and human health research, a recent undertaking. Several disciplines have to be involved in soils and human health research, such as soil science, geology, geography, anthropology, biology, agronomy, sociology, medicine, public health, etc.

EcoHealth is an emerging field of study researching how changes in the Earth's ecosystems affect human health, and it has many prospects.

Ecohealth examines changes in the biological, physical, social, and economic environments and relates these changes to human health. Examples of these changes and their effects abound. Common examples include increases in asthma rates due to air pollution, PCB contamination of game fish in the Great Lakes of the USA, and habitat fragmentation leading to increasing rates of *Lyme disease*.

Recently virulent new infectious diseases such as *SARS*, *Ebola virus*, *Nipah virus*, *bird flu*, *hantavirus*, and the actual *COVID-19*, all have been found to result from ecosystem changes created by humans. Unfortunately, these diseases have high death rates and very few effective therapies. Such experience makes clear that science does not have immediate answers for everything; science uses to be reactive. Scientists in less than a month determined the genome of *COVID-19*, and soon thereafter they could discover and prepare tests for its identification in infected persons. So far, 7 months after its appearance in China, no effective therapy has been developed. The primary mode of transmission for enveloped viruses wrapped in the bilipid membranes, as is the case of *COVID-19*, is by close contact with infected individuals. Viruses like *COVID-19*, however, are released to the environment by the host in the form as part of aerosols when he coughs, sneezes, and speaks and persist in the air, or in the water, or yet on surfaces after their deposition (i.e., fomites), long enough to come into contact with another host for further onward transmission (i.e., indirect transmission). Environmental engineers and scientists could play important roles in dealing with virus outbreaks and pandemics (Wigginton and Boehm 2020).

It is interesting to mention that in 2007 the US Geological Survey (USGS) developed a science strategy outlining the major natural science issues facing the nation in the next decade. The strategy consists of six science directions that focus on areas where natural science can make a substantial contribution to such six science directions, one of them being entitled “The Role of Environment and Wildlife in Human Health: A System that Identifies Environmental Risk to Public Health in America” aimed to “Continue to identify wild animal disease reservoirs and maintain critical knowledge about wild animal disease transmission to humans, drinking water contaminants, air-dust-soil-sediments-rock contaminants, pathogens in recreational water, and the use of wild animals as sentinels of human health. Fully integrate data holdings and environmental science expertise to produce a national database and atlas of geology and ecology-sourced diseases and toxicants. Partner with allied health science agencies to support spatially related health research” (In: Geology for Changing World 2010–2020: Implementing the US Geological Survey Science Strategy, Circular 1369, US Department of the Interior and US Geological Survey).

Ecohealth is bringing together physicians, veterinarians, ecologists, economists, social scientists, planners, and others to study and understand how ecosystem changes affect human health. *Ecohealth* strives to provide innovative, practical solutions to reduce or reverse the negative health effects of ecosystem change.

Humans constantly interact with the environment, and several interactions will affect the quality of life, years of healthy life lived, and health disparities. A healthy human body has to be mentally and physically sound. The natural interaction of humans and the environment can affect the ecosystems with consequences in biodiversity, climatic regulation, and natural resources essential for life.

On September 22, 2020, the *One Earth* journal reports the output of studies carried out by a team of scientists from the University of Queensland, in Australia.

Within 2000 and 2013, the significant areas of intact ecosystems estimated at around the area of Mexico, particularly of tropical and subtropical ecosystems, were moderately or intensively modified by anthropogenic actions. Actually only 25% of the Earth's surface can be classified as "savage area."

Public Health is the science and art of preventing disease, prolonging life, and promoting human health through organized efforts and informed choices of the society; organizations, public and private; communities; and individuals, analyzing the health of a population, and the threats are the basis for *public health*.

The "public" in question or discussion can be as small as a handful of people, or an entire village, or yet it can be as large as several continents, in the case of a pandemic. Also, the "health" in question or discussion takes into account the physical, mental, and social well-being. Health, according to the World Health Organization (WHO), is not merely the absence of disease or infirmity, and WHO defines "environment" in its relation with *health* as:

> All the physical, chemical, and biological factors external to a person and all the related behaviors.

Public health is interdisciplinary. For example, epidemiology, biostatistics, and health services are all relevant, and environmental health, community health, behavioral health, health economics, public policy, mental health, and occupational safety are other important subfields of *public health*.

Public health aims to improve the quality of life through the prevention and treatment of disease, including mental health. This is done through the surveillance of cases and health indicators and through the promotion of healthy behaviors. Common *public health* initiatives include promoting hand washing and breast feeding, delivery of vaccinations, the control of transmitted diseases, the distribution of condoms to control the spread of sexually transmitted diseases, and suicide prevention.

An example of *public health* threat is the actual coronavirus disease outbreak, whose origin and transmission likely occurred in an open food market in Wuhan, in China, in December 2019. The disease is called *COVID-19*, which stands for coronavirus disease 2019, and is caused by infection from the new coronavirus SARS-CoV-2 which is one of the multiple corona viruses that can affect humans.

The *COVID-19* outbreak was classified by the World Health Organization (WHO), in March 10, 2020. The disease spreads from person to person through respiratory droplets originated by cough or sneeze.

The WHO declared the outbreak to be a Public Health Emergency of International Concern on January 30, 2020, and nominated it as a pandemics on March 11, 2020. As of April 27, 2020, more than 2.99 million cases of *COVID-19* infection have been reported in 185 countries and territories, resulting in more than 207,000 deaths. In May 15, 2020, more than 4.5 million people worldwide had been infected, and more than 300,000 was the death toll; in June 26, 2020, more than 10 million people had been infected, and more than 500,000 was the death toll; in August 15, 2020, more than 21.5 million people had been infected and more than 750,000 was the death toll; and in December 20, 2020, more than 80 million of people had been infected and more than 1,75 million people have died. So far, USA, India, Brazil, Russia and Argentine are the most affected countries. Once again, science through the formulation and development of medicines and particularly of vaccines will come to assist humanity, and still in 2020 vaccines against COVID-19 virus have been produced and marketed. Never a vaccine had been so rapidly conceived, formulated, produced, accredited and marketed. The year 2020 could well be recognized as the year of science enthronization. Vaccination campaigns using from this moment one type of vaccine based on RNAm are already in progress, initiated in USA on December 14, 2020, in UK on December 8, 2020, and in EU countries on December 27, 2020.

Other examples of inevitable and calamitous diseases include SARS (severe acute respiratory syndrome, epidemic outbreak first reported in November 2002 in the Guangdong province of southern China and recognized in February 2003), MERS (Middle East respiratory syndrome, epidemic outbreak first reported in Saudi Arabia in 2012), H1N1 (the Spanish flu), V5H1 (the Avian flu), HIV (human immunodeficiency virus), and EBOVD (*Ebola* virus disease).

Experience has shown, from time to time, that man is not the only, neither the most powerful living being in nature. Man can put the other living beings at risk (e.g., contributing for climate changes and ecosystems changes), but they can put man at risk too.

It is appropriate to remember the quote of the Dutch philosopher Desiderius Erasmus Roterodamus (1469–1536): “No animal is more calamitous than man, for the simple reason that everyone is content with the limits of his nature, whereas only man is determined to overcome the limits of his.”

Science, although mostly in a reactive way – science is better to explain the past than the future, and is more made of doubts than certainties, is finding out solutions to fight such unexpected disease outbreaks caused, in the case of *COVID-19* by a nanosize natural dire being that acts like a sophisticated thief that penetrates the cells of the host, lives from them, and replicates. *COVID-19* virus still is scarcely known; it is invisible to the naked eye, although it is visible with other observation means, and it is highly insidious, contagious, and lethal. Virus activity in humans is the outcome of the improper interaction between man and the virus host such as wild animals. The greatest challenge for man is how to deal with the reciprocal cohabitation with the virus. The actual virus pandemic shows the ruling of the virus, and how he puts *public health* at risk, man getting fright by the sanitary, political, and social disorders caused by the virus. Also, it is important to recall that in specific situations, specific minerals can put *public health* at risk.

Modern *public health* practice requires multidisciplinary teams of *public health* workers and professionals. Those teams might include epidemiologists, biostatisticians, medical assistants, *public health* nurses, midwives, or medical microbiologists. Depending on the need, environmental health officers or *public health inspectors*, *bioethicists*, *geochemists*, *toxicologists*, and even *veterinarians* might be called on.

Returning to Medical Geology, firstly, it is necessary to show and demonstrate to the general public and to policymakers in particular, through examples characterized by notorious impact on *public health* and its good publicity in the mass media, the importance of Medical Geology; secondly, it is important to raise awareness and prepare researchers for a field of knowledge that is so strongly interdisciplinary that it should interest and involve people with professional training in diverse scientific areas, such as medicine, geology, biology, biochemistry, biophysics, mineralogy, geochemistry, hydrogeology, hydrochemistry, ecology, environment, food chemistry, nutrition, toxicology, pathology, epidemiology, etiology, territory planning, and economics.

About one dozen of books already have been published, and hundreds of scientific articles have been published annually in the scientific field of Medical Geology. There have also been eight MEDGEO international conferences on *Medical Geology*, the last one held in Moscow, in 2017, and the other one in Guiyang, Guizhou, China, in 2019. About 200 abstracts had been submitted to both conferences. However, it looks like that MEDGEO conferences continue to show much interest on GEO and less interest on MED. Attempts need to be made in order to achieve the required balance between both components.

The IMGA (International Medical Geology Association) gathers around 250 individual associate members from 43 countries and 21 chapters. It is in charge of organizing MEDGEO biennial international conferences and workshops. One of the first workshops was the 2005 Workshop International of Medical Geology entitled "Medical Geology in Brazil: Environmental and Health effects of Toxic on Materials Geological Factors" that was held in Rio de Janeiro, Brazil. The 30 contributions then being presented were published in 2010, Silva CR, Figueiredo BR, de Capitani EM, Cunha FG, being the editors. The IMGA is making great efforts to promote and train scientists in the emerging field of Medical Geology.

The MEDGEO 2021 will join the fifth ISEH (International Symposium on Environment and Health) and the sixth ICEPH (International Conference on Environmental Pollution and Health), joint meeting that will be held at the National University of Galway, Ireland, in August 2021. The MEDGEO 2015 (sixth International Conference on Medical Geology) was held in Aveiro, Portugal.

The growing importance given to the emerging Medical Geology has led to the exaggeration of designating specialists involved in studies that relate animal and human health to geological processes and products by "medical geologists" (Centeno 2017).

Hasan (2017) proposes the adoption of the term *geohealth* to replace the term *Medical Geology*, since it is all inclusive, has a wide scope, elegantly incorporates medical geography, and fits well with the total health concept; while Medical Geology focuses on geological processes and materials and their impacts on human and ecological health, the author suggests that the scope and definition of Medical Geology be expanded to include socioeconomic and public policy aspects since they influence an individual's or a community's health outcomes. According to Hasan et al. (2013), to actively pursue Medical Geology issues, the countries must have robust geoscience and environmental science communities, conscientious public health communities, sound economies, and favorable political atmospheres.

Science and technology are expensive being the taxpayers who pay both. To continue to justify such an effort, it is imperative that scientists pass on to the public information about what they are investigating and the reasons why science and the projects in which they are involved are important. Effectively, communication in science is a duty, and the publication of scientific texts in the form and content accessible to all is one way of doing so.

Historically the present century may remain as the century of new scientific fields, such as: biomedicine, science of interface between biology and medicine of interface; astrobiology, the science of interface between astrology and biology, having as main objective the identification of the origin of life; biotechnology, science of the interface between biology and engineering; and, of course; environmental medicine, science of the effects of the environment on health and its minimization if they are adverse; and environmental epidemiology, science of the effects between environmental exposure and the prevalence and incidence of diseases, depending on variables such as genetics, age, lifestyle, occupation, etc., can, in the latter two areas, certain knowledge and research results in the area of geosciences may play a relevant and determinant role.

The human and animal health impacts of pandemics, climate changes, volcanic eruptions, earthquakes, landslides, tsunamis, and hurricanes are actual and promising issues of Medical Geology.

The term *environmental medicine* was first employed by **Mö**ller (2000), and it was later used too by Fowles et al. (2005, 2013). For the last referred authors, the target of environmental medicine is the study of how the environment affects health, including the exposures characterization and the practice of how to minimize any adverse effects, the environment being the one directly related to the products and processes of geological origin. For the authors, the term *environmental medicine* is synonymous with the term *environmental health*. Human health impacts of environmental sciences have been dealt with by Jacobs and Porter (2012).

According to Olden and White (2005), in the last 25 years, there have been impressive advances in biological and social sciences. The discovery of genes and the sequencing of the human genome captivated the mass media, the public, policymakers, and researchers in biomedical sciences. It became clear that genetic defects were responsible for chronic diseases and that the identification of gene defects and gene therapy would lead to a cure and to the improvement of the population's health.

Like gene defects in humans, minerals have structural defects as happens with the so-called point defects, represented by atomic vacancies and atomic isomorphous substitution, which are quite common in natural *minerals s.s.*

As in *humans*, perfection (both internal and external) does not exist in minerals *s.s.*, the reason why the *individual minerals* belonging to a certain *mineral species* (e.g., *quartz*, *calcite*, *albite*, *microcline*, and *pyrite*) can be distinguished by particular crystallochemical characteristics. Each *individual mineral* is unique, as each *individual human* is unique. As a matter of fact, *mineral diversity* and *human diversity* do exist (Gomes 2015). Only the *equivalent synthetic forms* of some *minerals* could be produced almost free of structural defects.

Health diseases are currently called *health disorders*. Structural disorder in less or higher degree is common in minerals, and such disorder could be considered equivalent to diseases in humans, since *disorder in minerals* means less stability and durability. Humans have capabilities to adapt themselves to environmental changes, but unlike minerals, humans can change, too, the environment to good or bad for themselves. Environmental changes, particularly at or near the Earth's surface, could definitively affect rock and soil minerals, through the action of natural processes, such as physical, chemical, and biological weathering, leading to the elimination of some mineral species and to the creation of some other mineral species, the neoformed minerals, which result from the recombination of the chemical elements liberated through weathering. Clay minerals are the best example of how minerals respond to environmental changes, since as a rule they are formed at the Earth's surface where physical, chemical, and biological changes cyclically take place, and better than any other minerals, clay minerals have the capacity to adapt themselves and reflect eventual environmental changes. Such justifies the use, for instance, of clay minerals assemblages as important markers in the paleogeographical and paleoclimatic reconstructions. About these subjects many references exist in the specialized literature, one of the most recent works being herein mentioned (Bentz and Peterson 2020).

The so-called genetic edition is a promising technology, possibly the major revolution since the discovery of antibiotics, hoping to cure genetic diseases, particularly after the recently discovered CRISPR/Cas9 technique of genetic edition by the two scientists Charpentier E and Doudna J who won the *Nobel Prize of Chemistry 2020*. Using the enzyme Cas9 associated with a little fragment of RNA, the genetic material can possibly penetrate the living cells, and the enzyme could cut the DNA in a particular site localized by the RNA fragment that acts as a guide to the enzyme. The technique has a great potential to turn some plant and animal species more resistant to disease and to develop new therapies. Various clinical studies have been and are being planned, some already in progress, the main target being genetic diseases, such as cancer, sickle cell anemia, amyloidosis by transtiferritine, and Machado-Joseph disease. The genetic edition hopes to change the damaged DNA by a healthy DNA.

The uniqueness of individual humans is due to the uniqueness of their DNA. Regarding disease it can be differently manifested from individual to individual, and the same therapy and the same medicaments can produce varied effects in different individuals in terms of efficacy and side effects. Such varied effects also depend upon age, sex, and physical robustness of the individuals. For instance, in the USA, pharmacies sell the same medicine, as is the case of *zolpidem,* medicine used as sleep inducer, in different doses depending on sex, for man or for woman. In general, medicines and clinical trials are designed and addressed to the standard pacient man, as happens in the area of cardiovascular diseases.

Similar singularity can be found within individual minerals belonging to the same mineral species, which although having structures based on the same *crystalline unit cell* can be distinguished by trace physical and chemical details. Even within the same chemical element, metal or metalloid, singular chemical forms or species can exist, for instance, in Fe, Mn, Hg, Pb, Cr, As, Se, and S.

According to Olden and White (2005), the genocentric vision reflects a fundamental misconception of the disease process and has led so far to unrealistic expectations. Experience has shown that a single risk factor is rarely responsible for the development of most chronic diseases. Exposure to toxic substances and infectious agents contributes significantly to the development of chronic diseases, as well as behavioral factors such as smoking, excessive consumption of food and alcohol, and sedentary lifestyle. Also, poor diet and stress contribute to increasing disease susceptibility. Indeed, there is already substantial information indicating that many chronic diseases are caused by the interactions between genetic, environmental, and behavioral risk factors rather than by "bad genes."

The health status of humans and other animals depends greatly on the minerals present and bioavailable in the soil, absorbed and fixed in the plants, and in the water consumed which vary in composition depending on the geological, geographic, and climatic factors. It is assumed that the deepening of knowledge in cell biology, in molecular biology, and in the functioning of the human body will allow the development of drugs and other means that can cure diseases considered incurable and continue to increase life expectancy with quality. Also, deepening the knowledge of the biological functions of *minerals*, in particular of the so-called trace elements or trace minerals, is considered essential.

It is unthinkable to foresee limits to science. However, it must be remembered that the advances of science are so often conditioned by political, ethical, and religious decisions, well exemplified by the case of the controversy raised in many countries over the use of so-called stem cells (primitive and undifferentiated cells and which, as such, can differentiate into other cell types, which are capable of self-renewing and dividing indefinitely). *Stem cells* have been attributed to enormous therapeutic potential because they determine the genesis of all the cells and tissues of the human body (from the brain to the skin, from the liver to the bones, from the nerves to the heart, etc.). *Stem cells* exist in the bone marrow of adults, in the umbilical cord and placenta blood, and in very young human embryos (5 days old).

In any country the health sector comprises activities of paramount importance in social and economics terms. As an example, in Portugal, and according to Mello (2019), the health sector accounts for an annual business volume estimated at 27,000 million euros, involves about 89,000 enterprises, and employs 279,000 employees. Also, for the President of the Health Cluster Portugal, the health sector represents 27% of the total scientific publications, the sector being the one of higher scientific production.

References

Andrews JE, Brimblecombe P, Jickells TD, Liss PS, Reid B (2004) An introduction to environmental chemistry, 2nd edn, Blackwell Science Publishings

Bentz JL, Peterson RC (2020) The formation of clay minerals in the mudflats of Bolivian salars. Clays Clay Miner. https://doi.org/10.1007/s42860-020-00065-x

Boulos MNK, Le Blond J (2016) On the road to personalized and precision geomedicine: medical geology and a renewed call for interdisciplinarity. Int J Health Geogr 15:5. https://doi.org/10.1186/s12942-016-0033-0

Bowman CA, Bobrowsky PT, Selinus O (2003) Medical geology: new relevance in the earth sciences. Episodes J Int Geosci 26(4):270–277

Brevik EC, Burgess LC (eds) (2013) Soils and human health. CRC Press, Boca Raton

Brevik EC, Sauer TJ (2015) The past, present, and future of soils and human health studies. Soil 1:35–46. www.soil-journal.net/1/35/2015/, https://doi.org/10.5194/soil-1-35-2015

Buck BJ, Londono SC, McLaurin BT, Metcalf R, Mouri H, Selinus O, Shelembe R (2016) The emerging field of medical geology in brief: some examples. Environ Earth Sci 75:449

Bunnell JE (2004). Medical geology: an emerging discipline on the ecosystem-human health interface. EcoHealth 1:15–18. USGS, US Department of the Interior

Bunnell JE, Finkelman RB, Centeno JA, Selinus O (2007) Medical geology: a globally emerging discipline. Geologica Acta 5(3):273–281

Centeno JA, Finlelman RB, Selinus O (2016) Medical geology: impacts of the natural environment on public health. Geosciences 6(1):8. https://doi.org/10.3390/geoscinces6010008

Centeno J (2017) Medical geology: impacts of the natural environment on human health. MedGeo'17, 7th International conference on Medical Geology, Moscow, Conference materials, Plenary Lecture PL-01, 37

Chamley H (2003) Geosciences, environment and man. 1st edn., Elsevier Science Publishing Co, Amsterdam. ISBN: 0444514252

Davenhall B (2009) Your health depends on where you live. In: TEDMED 2009. TED Conferences LLC, New York. http://www.ted.com/talks/bill_davenhall_your_health_depends_on_where_you_live?language=en

Davenhall B (2010) The missing component: adding place when evaluating health risks (genetics+lifestyle+environment=risks) ArcUser, ESRI, Redlands 2010, Winterissue:1011. http://www.esri.com/news/arcuser/0110/files/geomedicine.pdf

Davenhall B (2012) Geomedicine: geography and personal health. Redlands ESRI, 2012. https://www.esri.com/library/ebooks/geomedicine.pdf

Davenhall B (2014) Place: the seventh vital sign. AMA J Ethics 16(2):135–137. http://journalofethics.ama-assn.org/2014/02/msoc1-1402.html

Davies TC (2010) Medical geology in Africa. In: Selinus O et al (eds) International year of planet earth. Springer Science+Business Media B.V.

Dissanoyake CB, Chandrajith R (2006) Inorganic aspects of medical geology. Z Dtsch Ges Geowiss 157(3):327–335

Dissanayake CB, Chandrajith R (2009a) Introduction to medical geology. Springer, Dordrecht, 297 pp

Dissanayake CB, Chandrajith R (eds) (2009b) Introduction to medical geology: focus on tropical environments. Erlangen earth conference series, Freiwald A (ed), Springer, Dordrecht, Heidelberg, 297pp. ISBN: 978-3-642-00-484-1, e-ISBN 978-3-642-00485-8

Duffin CJ, Moody RTJ, Gardner-Thorpe C (2013) A history of geology and medicine. Special Publications. Geological Society, London, 490pp

Figueiredo BR, Litter MI, Silva CR, Mañay N, Londono SC, Rojas AM, Garzón C, Tosiani T, Di Giulio GM, De Capitani EM, Dos Anjos JA, Angélica RS, Morita MC, Paoliello MB, Cunha FG, Sakuma AM, Licht AO (2010) Medical geology studies in South America. In: Selinus O et al (eds) Medical geology, International year of planet earth. Springer, pp 79–105. https://doi.org/10.1007/978-90-481-3430-4_4

Finkelman RB, Skinner HCW, Plumlee GS, Bunnell JE (2001) Medical geology. Geotimes, November 2001

Finkelman RB (2006) Health benefits of geologic materials and geologic processes. Int J Environ Res Public Health 3(4):338–342

Finkelman RB (2007) Health impacts of coal: facts and fallacies. Ambio 36(1):103–106

Finkelman RB, Orem WH, Plumlee GS, Selinus O (2018) Chapter 17: Applications of geochemistry to medical geology. In: Vivo B, Belkin HE, Lima A (eds) Environmental geochemistry, 2nd edn. Elsevier B.V, Amsterdam, pp 435–465

Finkelman RB (2019) The influence of clays on human health: a medical geology perspective. Clays Clay Miner 58(2), J Clay Minerals Soc. ISSN 0009-8604. https://doi.org/10.1007/s42860-018-0001-9

Fowles J, Weinstein P, Tseng C-H (2005) Environmental medicine. In: Selinus O (main ed) Essentials of medical geology. Burlington, MA: Elsevier Academic Press, pp 541–562

Fowles J, Weinstein P, Tseng C-H (2013) Environmental medicine. In: Selinus O (main ed) Essentials of medical geology (revised edition). Springer, pp 549–567. https://doi.org/10.1007/978-94-007-4375-5

Gomes CSF, Silva JBP (2006) Minerals and human health: benefits and risks/minerais e Saúde Humana: Benefícios e Riscos. Multiponto, 4000–299 Porto, 142 pp/158 pp

Gomes CSF, Silva JBP (2007) Minerals and clay minerals in medical geology. Appl Clay Sci 36:4–21

Gomes CSF (2015) Semelhança, Dissemelhança e Interdependência entre o Ser Humano e o Ser Mineral. O Liberal (editor), Câmara de Lobos, RAM, 371pp. ISBN: 978-989-8503-73-2

Hasan SE (2017) Total health initiative and medical geology: need for a fresh perspective. Medical geology-impacts of the natural environment on human health. MedGeo'17, 7th International Conference on Medical Geology, Moscow. Conference materials, Plenary Lecture KL-02, 38

Hasan SE, Finkeman R, Skinner CW (2013) Geology and health: a brief history from the pleistocene to today. In: Bickford ME (ed) The impact of the geological sciences on society, The Geological Society of America, Special paper 501, pp 155–164

Hochella MF (2002) Sustaining Earth: Thoughts on the present and future roles of mineralogy in environmental sciences. Mineral Mag J Mineral Sci 66(5):627–652

Hogan DE, Burstein JL (eds) (2007) Disaster medicine, 2nd edn. Lippincott Williams and Wilkins, Philadelphia

Holick MF (1995) Environmental factors that influence the cutaneous production of vitamin D$^{1-3}$. Am J Clin Nutr 61(suppl):638S–645S

Jacobs AM, Porter D (2012) Environmental sciences: health impacts. Kendall Hunt Publishing, Dubuque, 146pp. ISBN: 10.1465206493

Jaramillo-Nieves LJ, Finkelman RB (2012) Preface. Environ Geochem Health 34:153. https://doi.org/10.1007/s10653-011-9432-0

Keller EA (2002) Introduction to environmental geology. Prentice Hall, CDROM, Upper Saddle River

Komantina M (2004) Medical geology: effects of geological environments on human health. Elsevier Science Publishing Co, Amsterdam. ISBN: 0444516158

Korobova E, Romanov S, Silenok A (2020) Endemic diseases of geochemical origin and methodological approaches toward their prevention and elimination. Environ Geochem Health 42:2595–2608. https://doi.org/10.1007/s10653-019-00442-z

Läg J (1990) General survey of geomedicine in geomedicine. CRC Press, Boca Raton, pp 1–24

Landesman LY (2006) Public health management of disasters: the pocket guide. American Public Health Association, Washington, DC

Mason V, Andrews H, Upton D (2010) The psychological impact of exposure to floods. Psychol Health Med 15:61–73

Mello S (2019) Conhecimento, coesão e marca: a saúde 2030. Público 4 de Janeiro, 41

Miller AC, Arquilla B (2008) Chronic diseases and natural hazards: impacts of disasters on diabetic, renal, and cardiac patients. Prehosp Disaster Med 23:185–194

Möller L (ed) (2000) Environmental medicine. Karolinska University Press and Joint Industrial Safety Council, 327 pp

Olden K, White SL (2005) Health related disparities: influence of environmental factors. Med Clin N Am 89:721–738

Plumlee GS, Morman SA, Ziegler TA (2006) The toxicological geochemistry of earth materials: an overview of processes and the interdisciplinary methods used to understand them. In: Sahai N, Schoonen MAA (eds) Medical mineralogy and geochemistry. Reviews in mineralogy and geochemistry, vol 64. Mineralogical Society of America and Geochemical Society, pp 5–58

Plumlee GS, Ziegler T (2007) Chapter 7: The Medical Geochemistry of dusts, soils and other earth materials. In: Lollar BS (ed) Treatise on geochemistry, vol 9: environmental geochemistry, online edn. Elsevier, Oxford, pp 1–61. http://www.Sciencedirect.com/science/referenceworks/9780080437514

Plumlee GS (2009) Report from Ground Zero: How geoscientists aid in the aftermath of environmental disasters. Earth Mag 54:38–47

Plumlee GS, Morman SA, Cook A (2012) Environmental and medical geochemistry in urban disaster response and preparedness. Elem Mag 8(6):5

Plumlee GS, Morman SA, Meeker GP, Hoefen TM, Hageman PL, Wolf RE (2014) The environmental and medical geochemistry of potentially hazardous materials produced by disasters. In: Treatise on geochemistry, 2nd edn. chapter 11.7. Elsevier Ltd, Amsterdam, pp 257–304. https://doi.org/10.1016/B978-0-08-095975-7.0090-7-4

Sahai N, Schoonen AA (2006) Medical Mineralogy and Geochemistry. In: Rosso JJ (senior ed) Reviews in Mineralogy & Geochemistry. Geological Society and Mineralogical Society of America, 332pp

Sahai N, Schoonen AA, Skinner HCW (2006) The emergent field of medical mineralogy and geochemistry. In: Rosso JJ (senior ed) Reviews in mineralogy & geochemistry, vol 64. Geological Society and Mineralogical Society of America, pp 1–4

Salminen R (Chief ed), Batista MJ, Bidovec M, Demetriades A, DeVivo B, De Vos W, et al (2005) Geochemical Atlas of Europe. Part 1 – Background information, methodology and maps. Geological Survey of Finland

Sarkar D, Datta R, Hannigan R (eds) (2007) Concepts and applications in environmental geochemistry, vol 5 of the series “Developments in Environmental Science”, Published by Elsevier Ltd. ISSN: 1474-8177. https://doi.org/10.1016/S1474-8177(07)05001-2

Selinus O (2004) Medical geology: an emerging speciality. Terrae 1(1):A1–A8

Selinus O, Alloway BJ, Centeno JA, Finkelman R, Fuge R, Lindh U, Smedley P (eds) (2005) Essentials of medical geology: impacts of natural environment on public health, 1st edn. Elsevier Academic Press, Amsterdam, 1024pp. ISBN: 0126363412

Selinus O, Alloway BJ, Centeno JA, Finkelman RB, Fuge R, Lindh U, Smedley P (eds) (2013) Essentials of medical geology, 2nd edn. Springer, Dordrecht, 805pp

Selinus O, Finkelman R, Centeno J (2010) Medical geology: a regional synthesis. Springer, Dordrech, 392pp. ISBN 978-90-481-3429-8. https://doi.org/10.1007/978-90-481-3430-4

Silva CR, Figueiredo BR, de Capitani EM, Cunha FG (2010) Medical geology in Brazil: environmental and health effects of toxic on materials geological factors. 2005 Workshop International of Medical Geology, Rio de Janeiro, Brazil, Geological Survey of Brazil – CPRM Rio de Janeiro, 220pp

Skinner HCW (2000) Minerals and human health. In: Vaughan DJ, Wogelius RA (eds) Environmental mineralogy, EMU notes in mineralogy, vol 2. Eötvös University Press, Budapest, pp 383–412

Skinner HCW, Berger AR (eds) (2003) Geology and health: closing the gap. Oxford University Press, New York

Skinner HCW (2005) Biominerals. Mineral Mag 69(5):621–641

Warren HV (1965) Medical geology and geography. Science 148(3669):534–539. https://doi.org/10.1126/science.148.3669.534

Wigginton KR, Boehm AB (2020) Environmental engineers and scientists have important roles to play in stemming outbreaks and pandemics caused by enveloped viruses. Environ Sci Technol 54:3736–3739

World Health Organization. http://www.who.int/health_topics/environmental_health/en

World Health Organization: The role of WHO in Public Health

World Health Organization: Public Health Surveillance

World Health Movement: Public Health Actions

Zheng B, Wang B, Finkelman RB (2010) Medical geology in China: then and now. In: Selinus O, Centeno JA, Finkelman RB (eds) Medical geology-A regional synthesis. Springer, Dordrecht, pp 303, 392pp–327

Ziegler JL (1993) Endemic Karposi’s sarcoma in Africa and local volcanic soils. Lancet 342:1348–1351

Chapter 3
Historical Evolution of the Use of Minerals in Human Health

Celso S. F. Gomes and Michel Rautureau

Abstract The historical evolution of the use of minerals by humans for cosmetic and therapeutic purposes is most probably as old as the human species itself, naturally first applied on an empirical basis, and later moved to a scientific basis initiated with the dawn of scientific revolution, in the Renaissance. Such evolution is classified in this monograph into three periods: the classical antiquity involving ancient civilizations, Mesopotamian, Chinese, Egyptian, Greek, and Roman; the Middle Ages and Renaissance; and the modern and contemporaneous ages. In these periods, the interest for certain minerals as healing natural materials is reported and discussed. The "medicinal terras" of the Greek volcanic islands Lemnos, Chios, Samos, Milos, and Kimolos were particularly famed, as was the case of the "Lemnian terra," which became known as "terra sigillata" or "terra sealed" supposed to possess supernatural healing properties. On the other hand, certain arsenic-, lead-, and mercury-bearing minerals were soon identified by their poison and lethal properties. From the Renaissance onwards, the First and Second Scientific Revolutions and their particular outcomes in pharmacy and medicine have provided the explanations and justifications for both benefits and risks of minerals/human health interactions.

3.1 In the Classical Antiquity

The use of minerals for medicinal purposes is probably almost as old as the human species itself. Ancient civilizations, Mesopotamian, Chinese, Egyptian, Greek, Arab, and Roman, have used geological/mineral resources, for their therapeutic

---

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit "GeoBioTec",
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

M. Rautureau
Docteur d'État ès Sciences Physiques, Retired of University of Orléans, Orléans, France

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_3

value, as essential nutrients, as curative agents, and as amulets and talismans (Yu et al. 1995; Aziz et al. 2002; Limpitlaw 2004, 2010; Hasan et al. 2013; Duffin 2013).

Early in the antiquity, man identified and used few minerals, all of very simple composition, and most of metallic luster, such as copper (Cu), sulfur (S), silver (Ag), tin (Sn), antimony (Sb), gold (Au), mercury (Hg), arsenic (As), and lead (Pb).

In ancient China, minerals were used for therapeutic purposes. For example, in the Han Shan dynasty (c. 2500–2070 BC), the mineral *malachite* [$Cu_2CO_3(OH)_2$] was used as an amulet representing love, life, and fertility. In the time of Emperor Shen Nung (c. 2700 BC), known as the "father of Chinese medicine," and according to legend, Shen Nung tried poisons and the antidotes on himself and then compiled the catalogue or medical encyclopedia called "Pen Ts'ao" that lists hundreds of drugs derived from vegetable, animal, and mineral resources. Among the drugs is the plant cannabis referred to as "ma." The catalogue or list was updated and improved by emperors to come and became a famous medical publication containing references to hundreds of substances of mineral origin, for instance, *stibine* (Sb_2S), *cinnabar* (HgS), *calcite* ($CaCO_3$), *niter* (KNO_3), *melanterite* ($FeSO_4.7H_2O$), *sulfur* (S), and *talc* [$Mg(Si_4O_{10})_2(OH)_4$].

The Tibetan *Materia Medica* includes 2294 materials, of which 1006 are of plant origin, 448 of animal origin, and 840 minerals (Dharmananda 2012).

Davies et al. (2005) mention that during both the Song dynasty (1000 B.C.) and the Ming dynasty (fourteenth to seventeenth century A.C., more precisely from 1368 to 1644), lung disorders related to rock crushing and symptoms of occupational lead poisoning were recognized. The authors cite in Liang et al. (1998) the alchemist Chen Shao-Wei, in the Tang dynasty, stating that lead, silver, copper, antimony, gold, and iron were poisonous.

In China, the history of the disease and its therapy can be classified into three main periods: the pre-Confucian covering the Shang and Zhou dynasties (from about 1500 to 256 BC), the Confucian until the beginning of the twentieth century, and the post-Confucian up to the present. Confucius (551–479 BC) was a famous Chinese thinker and philosopher. Under the influence of Confucianism and Taoism (seventh and sixth centuries BC), Chinese medicine has become more based on natural phenomena and processes, with internal and external causes of disease.

According to the earliest records, it was believed that the diseases were caused by the spirits of ancestors and living beings involved in magic practices and to treat them it was necessary to use spells or make offerings to appease the spirits; later the causes of the illnesses were attributed to demons, and their treatment was the charge of the *shamans* who prescribed prohibitions and remedies of vegetal, animal, and mineral origin with the purpose of expelling the invaders. Also, according to Zheng et al. (2010) (*In*: Hasan S et al. 2013), the interaction between natural environment and human health is shown in two important books on Chinese traditional medicine: *Huang Di Nei Jing* (475 BC to 220 A.C.) is devoted to the cause and prevention of diseases and speculates on the relationship between diseases and water quality, soil, and climate; and *Lu Shi Chun Qiu* (239 BC) makes a clear description of the relationship between drinking water and health in China.

There are also references to the use of so-called medicinal earths or medicinal terras based on clay/mud in Mesopotamia, ancient Egypt, and ancient Greece to heal wounds and skin irritations, current practices in Mesopotamian culture (3000–2000 BC) and Assyrian-Babylonian culture (2000–300 BC).

Clay, a geomaterial of ubiquitous occurrence in shallow areas of the Earth, and therefore easily accessible and extractable, has been used by humans consciously as animals have always doing too but spontaneously since before the existence of historical records to satisfy a basic but fundamental purpose, to take care of their health. *Clay* is a natural aggregate of minerals, hence it is a rock, of fine granularity and earthy texture that, as a rule, develops plasticity when water is added to it in adequate quantity and that acquires good cohesion and mechanical resistance after being dried and more yet after being fired. In the clay composition, the fundamental constituents are so-called clay minerals, classified as hydrous phyllosilicates of both planar and nonplanar crystal structures. *Clay* is an important component of a rock called *sandstone* providing intergranular cohesion to it and used as building stone ever since, in temples and houses, the oldest ones found, for instance, in the town of Petra, capital of Nabantea, presently in Jordan, that flourished between first century BC and first century A.C., being famed the temples al-Khazneh and ed-Deir. At that time, Petra was an important local of commerce and passage of exotic products, precious stones, and spices with origin in India and Arabia to Greece and Roman.

The Nippur clay board or tablet in Mesopotamia, also known as the Mesopotamian Sumerian tablet, dating to about 2500 BC, and stored in the Museum of the University of Philadelphia, contains reference to the use of medicinal earths and to minerals *nitro* (KNO_3) and *halite* ($NaCl$) for therapeutic purposes, including for the treatment of wounds and inhibition of bleeding. The first Sumerian small clay tablets that did appear in Uruk, and dated around 3200 BC, contained just numeric annotations related with the administration of the goods from temples.

The earliest references to the use of clay in the form of mud for the treatment of gynecological affections are found in the *Lahoun* or *Lahun Papyrus* dating from the nineteenth century BC and only discovered in 1889. Also, the famous *Ebers Papyrus* dating from about 1500 BC describes the treatments (methods and doses) of some diseases using drugs based on about 500 substances, including *clay* and other minerals (especially *copper*, *lead*, and *antimony* minerals). *Malachite* [$Cu_2(CO_3)(OH)_2$] was reported in the treatment of wounds, ulcers, and eye diseases.

The *Ebers Papyrus* found in 1860 among the remains of a mummy in one of the tombs of Assasif, near Thebes, is the oldest medical document in the world and contains a compilation of references to remedies, partly magical and partly based on observation and experience, was bought in 1872 to the American collector Edwin Smith by the Egyptologist Georg Ebers who translated it (the reason why the papyrus is named Ebers) and is stored in the Library of the University of Leipzig, Germany.

In ancient Egypt, several minerals of medicinal interest were used: the so-called Nubian earth as anti-inflammatory in topical applications, mud or fango in foot and leg care, yellow ocher (natural clay and iron oxide/hydroxide mixture) in the treatment of dermatological affections, and *clay* and the mineral *natron* ($Na_2CO_310H_2O$)

in the mummification of corpses. Then, important knowledge of the interior of the human body was acquired by the application of dissecting techniques, which were necessary too for mummification.

The Egyptians had also used for therapeutic purposes (protection against the aggressiveness of the weather that caused irritations in the eyes and skin) cosmetic products based on the minerals *malachite* [$Cu_2CO_3(OH)_2$] and *galena* (PbS). The Egyptians also used mixtures of mineral pigments, animal fats, and resins in cosmetic applications and even synthetic minerals produced by them, now identified as *laurionite* [PbCl(OH)] and *phosgenite* ($Pb_2Cl_2CO_3$), the preparation of which is reported by Carretero and Pozo (2007), to obtain cosmetic products of white color or of gray color, in the latter case with addition of *galena* (PbS) that has the black color of lead.

It should be noted that Cleopatra (69–30 BC), Queen of Egypt, used, among others, cosmetics made from minerals and mud from the Dead Sea for aesthetic treatments. Today, it is known that the muds that cover the bottom of the Dead Sea, of black color and good plasticity, saturated in mineral salts and rich in *sulfur* and organic compounds, are used in topical applications (*mud therapy* and *pelotherapy*).

The Dead Sea is a unique place on Earth, characterized by stillness, silence, and atmosphere richer in oxygen and bromine than normal with about 330 days/year of singular sun and light, occupying a tectonic depression whose base reaches 416 m below sea level and which is crossed by the Jordan River. The Dead Sea is actually an endorheic lake with great salinity (about 320 grams/liter, i.e., approximately ten times greater than the salinity of the Mediterranean Sea), salinity that allows people to float on the surface of the water, with concentrations of minerals Mg, Ca, Br, K, and others higher than those found in other seas and oceans.

From ancient Greece to Roman, medieval, Renaissance, modern, and contemporary times, there are records on the therapeutic, nutritional, and cosmetic use of clay or of products in which clay participates. Already in ancient Greece, Hippocrates (460–377 BC), to whom was given the epithet “father or founder of medicine” in his book entitled *On Airs, Waters and Places*, and also Aristotle (384–322 BC), who devoted part of his life to biological research, produced interesting information about “medicinal earths” or “medicinal terras.” Also, in this same book, he recognized that health and place are causally related.

The “medicinal terras” of the Greek volcanic islands Lemnos, Chios, Samos, Milos, and Kimolos (Bech 1987, 1994, 1996, 2010, 2014) were particularly famous. The island of Samos is also famous because Aristarchus of Samos (c. 310–230 BC), a Greek scholar, astronomer, and mathematician born in the island, was the first to assume the heliocentric model that placed the Sun at the center of the known universe with the Earth revolving around it, eighteen centuries before Nicolaus Copernicus (1473–1543) being credited with the creation of the heliocentric model of the universe.

The “Lemnian terra,” in particular, which was supposed to possess supernatural healing properties, after being extracted during an annual ceremony was molded into small cylinders, troches, or tablets, each having a stamp-like imprint of the goddess Artemis (Diana, for the Romans), by what became known as “terra sigillata,” or “terra sealed,” or “terra sphragis,” or “earthen coin.”

According to Retsas (2016), “The therapeutic use of certain earths (medicinal earths or medicinal terras) and metals is well documented in the works of Hippocrates, Dioscorides and Galen and was still practiced in the eighteenth century by eminent physicians such as Sir Hans Sloane. Also, mercury and arsenical compounds have been used since Antiquity, the latter finding application in our times in the successful treatment of ‘acute promyelocytic leukaemia.’”

Figure 3.1 shows the image of a troche of *Leminia terra rubra* from the medicine cabinet of Sir Hans Sloane, with 23 mm of diameter (Natural British Museum, London).

Pliny the Elder (24–79 A.C.) in Chapter XIV of Book 35 of his *Natural History* says that the red sealed *Lemnian earth* was much appreciated and was part of all the usual antidotes. He also mentions in other books its use as a treatment for dysentery and as an ointment around the eyes to relieve pain and inflammation.

The Romans dedicated much appreciation to the beneficial use for the health of natural thermal waters in the so-called hot springs where mud was also used. They were famous the baths and the muds of Aqua Tabellicae already used in pre-Roman times, and that came to be called Aqua Augustae. Mud from the Aqua Patavinae spa was also used by Nero for the treatment of gout and reconstructed in the fourteenth century by the Republic of Venice. Much later in 1353, Giovanni Dondi (1330–1388) of Padua, in the book *De fontibus calidis agri Patavini*, describes the muds (“hot muds” or “hot fangos”) and the baths or thermal baths that came to be denominated by Abano Bagni and from 1930 by Abano Terme.

Fig. 3.1 Troche of *Terra Lemnia rubra* from the medicine cabinet of Sir Hans Sloane, with 23 mm of diameter. (Natural British Museum, London)

The Greek physician Pedacio Dioscorides Anazarbeo (c. 41–90 A.C.), surgeon of Nero and the Roman Legions, says in his book *De Materia Medica* (five-volume work dedicated mainly to plant substances but also includes the therapeutic use of stones metal, earth, and water, and that it was the great reference of medicine in the millennium and a half that followed its publication) that the *Lemnia's terra* is extracted from a hole in the island of Lemnos and that after being cleaned and mixed with goat blood was molded in the form of tablets marked with stamps that had the figure of a goat. Taken with wine, the small tablets were very effective against deadly poisons.

The same Dioscorides also refers to the Samian terra of the island of Samos, in which it distinguishes two varieties, one denominated collyrion used like "eye salve" and another denominated *aster*. In volume V of *De Materia Medica*, in addition to the so-called medicinal terras (*Lemnian terra* and *Samian terra*), there are therapeutic benefits of rocks (*limestone*, *pumice*, *serpentinite*, *ocher*) and minerals (*chrysocolla*, *azurite*, *cinnabar*, *calcite*, *realgar*, *orpiment*, *gypsum*, *hematite*, *magnetite*, *turquoise*, *siderite*, and *asbestos*).

Galen of Pergamum (129-c.200 A.C.), the most prolific and influential physician during the Roman Empire and who contributed decisively to the development of pharmacology, describes the *Lemnia's earth* or *Lemnia's terra* in his work or treatise *Simplicium medicamentorum temperamentis ac facultatibus* as a soil of reddish color that dyes the hands of reddish and that comes from the top of a hill of color equally reddish located near the city of Hephaestias. Galen mentions that *Lemnian earth* is astringent, a property that presently could be explained by the presence of *alum*, the name of a mineral group comprising aluminum-rich sulfates, for instance, *K-alum*, or $KAl(SO_4)_2.12H_2O$, known by its clear astringency, identified together with the clay minerals *montmorillonite*, *kaolinite*, and *iron oxy-hydroxides* too by Hall and Photos-Jones (2008). Also, Photos-Jones et al. (2017) had carried out mineralogical, chemical, and microbiological analyses on historical samples of *Lemnian sphragides*, and relatively to the microbiological analyses significant antibacterial properties against the Gram-positive pathogenic bacterium *Staphylococcus aureus* were found, but no such effect against the Gram-negative *Pseudomonas aeruginosa*. And Venieri et al. (2020) have studied both chemical and mineralogical properties as the antibacterial activity of six samples of "terra sigillata" from the Pharmacy Museum of the University of Basel. Only the sample of a red Armenian bole was found to be antibacterial against both Gram-positive and Gram-negative bacteria.

Twice in years 162 and 167, Galen sought to visit the "mine" where the extraction of the earth was made, as well as observe the way of preparation of the tablets. Having succeeded only in the attempt of 167, he then acquired about 20,000 tablets to experiment on his patients.

According to Hall and Photos-Jones (2008), Photos-Jones and Hall (2011), Photos-Jones et al. (2016), and Retsas (2012), "Lemnian terra," a reputed antidote against poisons and bite of vipers, apparently continued to be used until the nineteenth century and consisted of the first "Pharmacopoeia of the Royal College of Physicians of London" (Thompson 1914).

The search for the natural occurrence of the legendary "Lemnia's terra" was recently the subject of a roadmap carried out by Bech (2014), who described, in the speech given to get the title of Doctor Honoris Causa at Miguel Hernandez University in Elche, Spain, the results of that roadmap in 1993. Lemnos is a Greek island situated in the NE of the Aegean Sea at a strategic crossroads of passage from the Black Sea to the Mediterranean Sea and from Europe to Asia. According to Hall and Photos-Jones (2008), it was in an area to the southeast of Kotsinas that *Lemnian earth* had been most likely extracted. More precisely, it was on a hill of the Mosiclos volcano where Bech found the trenches from which the "Lemnian terra" had been extracted, and Bech found that it was part of the weathering layer of trachytic rock, consisting of two horizons, one reddish-colored below and other white-gray above.

According to Robertson (1986), "terra sigillata" is one of the earliest historical examples of commercial therapeutic agents that were distributed throughout almost the entire Western world.

During the Byzantine Empire, the so-called medicinal earths have undergone a long period of obscurity, and were the Ottomans who dragged the famed *Lemnian earth* from the obscurity of classical encyclopedias. It was the French traveler Pierre Belon du Mans who visited Lemnos in 1546 and discussed Lemnian earth in his book *Voyage au Levant: Les observations de Pierre Belon du Mans de plusieurs singularities & chosen mémorables trouvées en Grèce, Turquie, Judée, Egypte, Arabe & autres pays étrangers*, dated of 1553. He found 18 varieties of seals for 4 types of earth. Belon mention the name *tin-i makhtum* and the name *tin i machon* that the Ottomans and Arabic, respectively, gave to the Latin name *terra sigillata* and *terra lemnia.*

Hippocrates (460–370 BC), certainly the most influential physician in the history of European medicine, makes about 60 references to the therapeutic use of various "terras." In his book on *Natura muliebri liber* or *Female Nature*, the use of the "black terra of Samos" ingested after being dispersed in water is recommended to resolve a certain affection of the uterus (Retsas 2016). The Hippocratic Corpus (a collection of around 60 ancient Greek medical works closely associated with Hippocrates and ranging in date from the fifth to the fourth century BC) also refers, for example, to the negative effects (corrosive, caustic, etc.) due to arsenic minerals, identified very soon as *orpiment* (As_2S_3) and *realgar* (As_2S_2), then widely used as therapeutic agents. Recently, the International Agency for Research on Cancer acknowledged that arsenic compounds are carcinogenic (IARC 1987).

Hippocrates was designated the "father of medicine," especially from the Renaissance until the nineteenth century, not because he was its founder, but because he was who established the foundations that served as the basis for medicine over almost two millennia. The compilation of his works and of his followers of the following generations was brought together in the so-called Hippocratic Corpus which was the matrix of European medicine until the end of the eighteenth century. The texts entitled "Epidemics" report cases of patients assisted by Hippocrates and contemplate information from the surrounding natural environment of these patients.

Hippocrates and his followers value the study of the human body, its organs and functions, and the influence of nature ("physis") on disease. Hence, the physician was called “physicist,” as it is still called “physician” in English, having the function of assisting and perfecting the nature which, in a universal sense, encompasses cosmic nature and order and, in a particular sense, encompasses the individual order nature that is of most interest to medicine and is explained by the combination of the *four humors* or fluids circulating in the human body – *blood*, *lymph*, *yellow bile*, and *black bile* – each of which corresponds to one of the four primordial elements (*air*, *water*, *fire*, and *earth*) and has associated with itself a quality (*hot*, *cold*, *moist*, and *dry*). Health corresponded to the correct balance of humors and to the harmonious functioning of organs, each of which contributes to a function of the whole. Conversely, the disease was the result of the imbalance of the humors or by excess or defect of one of the humors. Hence, the function of therapy consists mainly of restoring the good proportion between humors (*In:* Cardoso 2017a, b).

Hippocrates did recognize that human health and the place where we live are casuistically related and that environmental factors affect the distribution of disease (Läg 1990; Foster 2002). In his treatise *On Airs, Waters and Places*, Hippocrates pointed out that, in certain circumstances, the water that occurred associated to iron, copper, silver, gold, sulfur, and bitumen was not to be used for all purposes. The term “bad waters” was defined as “waters of marshy and stagnant grounds, i.e., without circulation or renewal.” On the contrary, the term “good waters” is those that run or flow on high grounds. It is interesting to note that it was only after about 2200 years that several diseases were found to be the result of microorganisms present in “bad waters.”

The relationship between water and health quality was well expressed in the book of Hippocrates, in the paragraph “Whoever wishes to investigate medicine properly must take into account several aspects … must consider the quality of water, because differing them in taste and weight should also differ a lot in quality.”

Hippocratic medicine, a medicine with scientific basis and method on the natural sciences – classification of the type of disease, description of the disease, analysis of the evolution of the disease, and adequate means of treatment – coexisted with traditional forms of religious and magical medicine, both strongly rooted in the popular strata. The professional dedication and ethical behavior of Hippocrates are still recognized today by the medical community through the so-called Hippocratic oath. The doctors to be able to exercise must swear and fulfill the words then written by Hippocrates:

> I swear by Apollo and Asclepius, by Hygeia and Panacea, and by all gods and goddesses, by taking them as witnesses, that I will fulfill this oath and commitment, according to my strength and understanding ….

Aristotle (384–322 BC) provided the first known reference to the deliberate ingestion by humans of soil, or clayey soil, or yet clay for therapeutic and religious purposes.

Theophrastus, a disciple of Aristotle who developed an empirical approach to natural history, in his book *On Stones*, the first scientific publication dealing with stones, industrial minerals, and artificial products of these derivatives, mentions four types of *earths* or *terras*: “Melos’s terra” or “Milos’s terra,” “Cimolia’s terra,” "Samia's terra," and "Tunphaic's terra," all considered important from the applied or "industrial" point of view. It is now known that the three *terras* above referred to are clays and that the fourth *terra* referred to is *gypsum* ($CaSO_4.2H_2O$).

The "Cimolia's terra," which is now known to consist of the clay mineral *calcium montmorillonite*, occurs in two varieties, white and red, both extracted on the Greek island of Kimolos. Similar *terras* or *clays*, also used at this time, occur in the Greek islands Chios (now Stalimene, traditionally considered Homer's homeland), Milos, and Lemnos.

Among the most famed medicinal clays, the "Bolus Armenus," the healing clay that occurs inside caves in the mountains of Cappadocia, ancient Armenia, and today Turkey, deserves a particular mention. Historically, this clay of reddish color, finely grained and soft touch, and used as an astringent prescribed to combat diarrhea, dysentery, hemorrhage, etc., was worthy of references by Theophrastus (c. 373/368–288/284 BC), Dioscorides (c. 41–90 A.C.), and Pliny the Elder (23–79 A.C.). Similar clay but with other origins was and continues to be used, under the name "Armenian bole," as is the case of the clay used as pigment, as a base for oil painting and gilding (application of gold leaf on pieces of carved wood, common, for example, in altarpieces and church altars), and for bookbinding.

In Roman times, the Greek physician Pedacid Dioscorides Anazarbeo, a surgeon of Nero and the Roman Legions, in the book V of his *Materia Medica* mentions 99 inorganic substances such as antimony, asphalt, calcium, sodium, sulfur, carbon copper, iron, lead, zinc, arsenic, mercury, and soils (Lev 2010). The "terra of Lemnos" called *morochthos*, a white clay that was medically used to stanch blood and to treat wounds, was mentioned too (in Robertson, 1986). According to this author, to this "Lemnian medicinal terra" was attributed supernatural healing properties. As aforesaid, the clay after being extracted during an annual ceremony was then shaped into small cylinders or torches and marked, sealed, or stamped with the image of the goddess Artemis, hence being known as "terra sigillata."

For Dioscorides, all "earths" or "terras" used medicinally are characterized by having properties of drying and occlusion of the pores depending on the type of application and of the mode of preparation. Dioscorides recommended the use of "Samos's terra" which is now known to be rich in borates, mixed with milk, for the treatment of ulcerated eyes. By the mid-twentieth century, the mixture of *boric acid* (H_3BO_3) and anhydrous *borax* ($Na_2B_4O_7$) was used as eye buffer (Martindale 1982, p. 337).

Also, Gayo Pliny Segundo, known as Pliny the Elder (23–79 A.C.) and author of the book *Historia Naturalis*, described the use of clays, some of volcanic origin with occurrences near Naples, especially as medicines for the stomach and intestines. Pliny the Elder was a famous Roman naturalist who died in Pompeii during the eruption of Vesuvius due to poisoning by the sulfur dioxide emitted by the eruption. This happened when he went to investigate the typology of the volcanic eruption that ended up destroying Pompeii. It was an eruption with an explosive character and a strong ejection of pyroclastic materials, essentially of a pythiatic nature, to which later the volcanologists attributed the name Plinian volcanism. Pliny the Elder, in one of the 37 volumes of the book *Historia Naturalis*, describes the use of clay, more precisely volcanic mud, to cure stomach and intestinal problems. It presents a list of terras or medicinal clays: the “Chios’s white terra” with properties similar to those of the “Samos’s terra,” used mainly in cosmetic applications; the “Selinute’s white terra” with similar applications to the “Chios’s white terra”; and the “Pnigitis’s terra” with medicinal properties similar to those of the “Cimolia’s terra.” It is probable that the “Chios’s terra” corresponded to the clay that came to be denominated *kaolin* and the “Pnigitis’s terra” corresponded to the clay that came to be denominated *bentonite* (Novelli 2000).

Galen (131–201 A.C.), a Greek physician born in Pergamum, describes the *medicinal terras* then used, for example, to combat gastrointestinal affections; refers to its therapeutic properties, organoleptic characteristics, and other properties; and shows how to recognize them. Galen described the “terras” as soil types that in contact with water “dissolve” producing viscous clay, visited the island of Lemnos to observe the processing of sealed discs (“terra sigillata”), and transported to Roma a great number of discs to treat illustrious patients. Then “sealed terras” were used in the treatment of several gastrointestinal disorders. Also, according to Galen, apart from the simple and proper use of the famous “terra of Lemnos,” this could enter into the composition of the so-called theriaca, an antidote for the bite of vipers and which contained about 60 additional components. Galen dedicated two books to “Theriaca” (Nutton 2004, p. 246). Galen evaluated the effectiveness of the antidote using two groups of chickens, one fed with *theriaca* and another not, but both exposed to bites of vipers, having verified that the group previously fed with *theriaca* survived unlike the other group.

Recent analyses by X-ray diffraction showed that the “Lemnos’s terra” consists of the clay minerals *montmorillonite* and *kaolinite* assessed in 40% and 30%, respectively, in addition to *alum*, $KAl(SO_4)_2.12H_2O$, making up 20%, and *hematite*, Fe_2O_3 (Hall and Photos-Jones 2008; Photos-Jones and Hall 2011, quoted in Paximadas 2014). The strong adsorbent and absorbent power of *montmorillonite* is well recognized, as it is the adsorbent capacity of *kaolinite*, and the astringent and antibacterial power of *alum*.

Galen, continuator and systematizer of Hippocratic medicine, gave strong impetus to science and medical art. Of the approximately 400 texts of the so-called Galenicum Corpus, the following treatises stand out: *The Natural Faculties*, *The Therapeutic Method*, *The Use of Body Parts*, and *On Mixtures and Properties of Simple Drugs*. This last treatise comprises eleven books, and the book IX entirely dedicated to “inorganic and mineral substances registered for their pharmacological properties” is devoted exclusively to drugs or simple drugs, recognized for having active ingredients of terra and stones harvested in various areas of the Eastern Mediterranean. The classification and description of these mineral medicines for pharmaceutical use comprises *Earths or terras*, *stones* and *metals*. According to this sequence, Galen mentions the types of *terras* found in various regions of Greece, the famous *Lemnian* and *Samian terras* included; then refers to stones according to color and ability to be milled and prepared as various types of clay with pharmaceutical properties; finally, are presented the mineral medicines, mineral substances used as drugs, and named “metallika pharmacy,” *lead* and *copper* included.

3.2 In the Middle Ages or Medieval Period

In the history of Europe, the Middle Ages or medieval period lasted from the fifth to the fifteenth century. It began with the fall of the Western Roman Empire and merged into the Renaissance and the Age of Discovery. The Middle Ages is the middle period of the three traditional divisions of Western history: classical antiquity, the medieval period, and the modern period. The Middle Ages is itself subdivided into three periods: the Early, the High, and the Late Middle Ages.

Following the fall of the Western Roman Empire, Europe went through a period of education and science decline during the Early Middle Ages (500–1000 A.C.). In the Early Middle Ages, the Arabian invasions brought important changes in culture and civilization in Europe, particularly on education.

In the so-called monastic period, education was provided in monasteries, such as Monte Cassino in Italy, S. Victor de Cluny in France, and Canterbury in England. About 800, with Carlos Magno, Emperor of the Occident, education had benefited of a kind of renaissance.

In the Middle Ages from the fourth to the fourteenth century, in an early period called Byzantine Empire (also known as the Roman Empire of the East) continued the extensive use of “medicinal terras” that had been used in the Greco-Roman period, being used among other varieties the so-called *Creta sutoria*, *Lutum pavimenti*, and *Alana gleba* (*In*: Carretero and Pozo 2007). Effectively throughout the Middle Ages the use of “sealed terras” to combat the plague epidemics has continued.

In Europe alone, between 1348 and 1351, the epidemic called the Black Death, which advanced from east to west and then to the north, will have wiped out a third of the population. The epidemic “Black Death” which was fulminating was transmitted by rats and fleas, developed in the soiling that prevails in inhabited places, and in the lack of public, collective, and individual hygiene. It was in the cities that the greatest number of deaths occurred, given the conditions of overpopulation, promiscuity, and insalubrity.

As the decadence of the Byzantine Empire was happening, the Arab or Islamic Empire was developing. The Iberian Peninsula would have been invaded in 711 by Arabs from North Africa who crossed the Strait of Gibraltar.

The baths or thermae, then ruined, left by the Romans, were rebuilt and revived, and the public and private baths were organized. Then the *mosque* and the *hammam* (the *bathhouse* and the *bath*) were completed: man could be purified by praying and bathing.

The doctor Al-Zahrawi, also known as Abulcasis (936–1013), born in Cordoba (then the main center of knowledge in Europe) and to whom frequently the Caliph asked for help, became a distinguished physician, surgeon, and pharmacologist and bequeathed to subsequent generations of physicians a 30-volume *Kitab al-Tasrif* encyclopedia, translated into Latin by Gerard de Cremona during the twelfth century, in which the experience gained over 50 years was divulged or revealed.

The chapter XXI-Magal was dedicated to the mineral panaceas used in the treatment of diseases of the mouth and teeth. Among those panacea, *alum* (hydrated aluminum and potassium sulfate), *borax* (sodium borate), *clay*, *arsenic salts*, *copper salts*, *salt*, *lapis lazuli*, *limestone*, and *vitriol* were referred to. The last chapter "On Surgery," published in several languages, was a reference for centuries. In his 300 pages, there are drawings and descriptions made by himself of more than 200 instruments that he used in the surgeries. He created, for example, hooks for unblocking artery clots, gynecological forceps, cauterization instruments, and for crushing urethra stones before removing them.

Before Al-Zahrawi, another physician, Al-Razi, born in 864 near to what is now Tehran, left more than 200 scientific works, among them a Treaty on Smallpox and Measles which, for centuries, was a reference work in the universities, and administered mercury to monkeys to prove that it could be used in humans. Arab doctors Avicenna (980–1037) and Averroes (1126–1198), the first born in Afshama, Persia, and the last born in Cordoba, encouraged the use of medicinal mud and classified various types of mud.

Avicenna, known as the prince of physicians, the initiator philosopher of the alchemist school whose influence lasted until the eighteenth century, and whose name corresponds to the Latin transcription of the Latin name Ibn-Sînâ, in his book *El Canon* refers to some remedies and the respective prescriptions. In this book, Avicenna also reports 12 types of clay (local varieties such as *Lutum corascenum*, *Alnisaburi*, *Alcori*, *Abaira*, and *Alcabrusi*), some for internal use and others for external applications. Avicenna reports that certain clays that are ingested can cause obstructions in the digestive tract and that other clays are beneficial for treating rheumatic diseases involving joints, for anti-poison treatments, etc. In his reflections on theoretical alchemy, Avicenna explains how not only inorganic substances, such as precious stones and metals, can be formed from the four traditional elements of Greek philosophy (*water*, *earth*, *air*, and *fire*) but also the four humors (*blood*, *lymph*, *yellow bile*, and *black bile*) of ancient medicine.

Alchemy thus abolished the boundary between the inorganic and the living and in turn became the foundation or basis of medicine and metallurgy. One of the objectives of alchemy, which was confused with chemistry until the seventeenth century, was transmutation, that is, the transformation of metals into gold by employing secret and magical processes.

In the twelfth century the book *Rgyud Bzho* or *Four Tantras*, which is a compilation of *Sowa Rigpa* known as traditional Tibetan medicine and incorporates some principles and techniques of other systems of traditional medicine, Greco-Arabic and Chinese, mentions that minerals were involved in formulations, usually associated with plants, 28 minerals still in current use in Bhutan (Yeshi et al. 2018).

The physician Ibn-Rushd, better known as Averroes, has extensive work published, much of it with another Al-Andalus physician named Ibn-Zuhr, known as Avenzoar, born in Seville in 1091. Ibn-Zuhr as other medieval Islamic physicians countered the “mood theory” particularly developed by the Roman physician Galen and who continued to dominate Western medicine. It was thought that the fluids circulating inside the body had to be in balance, otherwise the disease would appear. Hence, the said balance sought to be attained by means of bleeds and purges. Ibn-Zuhr demonstrated that the *scabies disease* was caused by an external agent, a *mite*. Later, the Arab doctor Ibn al-Baitar (1197–1248), born in Malaga, was the author of a book of pharmacology where he published eight types of clay-based *medicinal terras* for therapeutic and cosmetic uses.

It were the Arab doctors who in the eleventh century introduced the medicinal use of the so-called bezoar in Western medicine, a type of hard concretion formed in the digestive tract of certain animals, such as goat and porcupine, composed of inorganic matter (e.g., phosphates and carbonates) and organic (e.g., indigestible fibers of vegetables and fruits), not being a true mineral or rock. *Bezoar*, a term that is supposed to derive from the Arabic word “badzehr” or from the Persian word “panzehr,” both meaning anti-poison or antidote, was widely used until the seventeenth century as an antidote to arsenic-based poisons used in particular in European courts, reaching values higher than gold, but never having been explained the antidote action. From the end of the seventeenth century, the use of *bezoars* declined and the respective medicinal effects were discredited, and counterfeiting also contributed to this effect, since demand was much higher than supply. In the seventeenth century, in Goa, a group of Jesuit monks produced artificial *bezoars* sold to wealthy British persons.

The Portuguese played an important role in the bezoar trade. Several authors, for example, Williams (1986) and Barroso (2013), report relevant information on the history and application of *bezoars*.

San Alberto Magno (1200–1280) in his book *Minerabilus*, published in 1250, refers to the use of some minerals for therapeutic purposes.

The Portuguese Pedro Julião Rebolo, known in the academic world by Pedro Hispano (c. 1205–1277), a physician, philosopher, mathematician, and teacher and who became Pope John XXI, in his book *Treasure of the Poor* presents several recipes created by himself or by other authors in which some minerals, metals, and animal concretions participate. Pedro Hispano mentions five recipes extracted from the book *De Lapidibus* of Marbode, bishop of Rennes (1035–1123), which involve geological materials, the book being one of the most popular books in medieval literature.

In the famed *Lapidaries* of Alfonso X (1221–1284), a Castilian king known as “The Sage,” there are references to the use of minerals for medicinal applications. The first lapidary is a translation from the Arabah to the Castilian of the lapidary of Abolays, which would already be a translation of the Chaldean into Arabic. Alfonso X was a singular king of esoteric dimension who sought to combine wisdom and faith and who strengthened the so-called School of Translators, with nuclei in Toledo and Seville, dedicated to the translation of Arabic works on astrology, mathematics, and medicine. Also, in 1388, Giovanni Dondi in his book *Tractatus de fontibus calidis agri patavini* recommended the topical application of mud to treat subcutaneous affections.

Still in the Middle Ages, the first universities were created in Paris, Bologna, and Oxford, during the twelfth and thirteenth centuries. The first university in Portugal was created in 1290 in Lisbon.

3.3 In Modern and Contemporaneous Ages

In the modern age, which dates from the fifteenth to the eighteenth century, in an early period called the Renaissance or the dawn of the modern age, the science of nature or natural history and man, unlike religion, became the protagonists, art, science, and literature being valorized.

At the turn of the sixteenth century, an authentic revolution emerged in Europe – the so-called First Scientific Revolution, a concept used by historians to describe the emergence of modern sciences: mathematics, physics, astronomy, biology, etc., 1543 being the date of the traditionally assumed beginning of the *First Scientific Revolution*, based on the application of the so-called scientific method characterized by three components (observation, experimentation, and logical reasoning).

Science progressed relentlessly and changed the conception of man and the world, breaking the connections to theology that hitherto existed. Among others, Nicholas Copernicus (1473–1543), Michelangelo (1475–1564), Francis Bacon (1561–1626), Galileo Galilei (1564–1642), Johannes Kepler (1571–1630), René Descartes (1596–1650), Francesco Redi (1626–1698), and Isaac Newton (1642–1727) were proeminent in key developments in science, the arts and culture.

Not only did the world changed, but it also expanded dramatically through the discoveries made by the navigators of the Iberian peoples. If the navigators expanded the world, the Polish astronomer Nicolaus Copernicus enlarged the universe by placing the Earth in its place within the cosmos, being that it revolves around the Sun and not the other way. In turn, physicians and anatomists develop the physical exploration of the human body. The interest in knowing and mapping the interior of the human body brought together anatomists and artists. The anatomists dissected and wrote down what they saw. The artists drew and composed what they observed.

Of the artists who studied the human anatomy featured goes back to Leonardo da Vinci (1452–1519) who designed not only the inert body or corpse but also the body movement. The harmony of the human body is excellently exhibited in the drawing "Vitruvian Man." Leonardo da Vinci was a man of very different talents, particularly divided between arts and science. In the fields of anatomy, optics, and thermodynamics, as inventor and painter, he highly valued life by writing "Who does not give value to life does not deserve it," life that must be sustained by a fruitful activity expressed in his aphorism "iron oxidizes if not removed the stagnant water loses purity and freezes with the cold." As anatomist and dissector, Leonardo da Vinci tried to understand the human body functioning, being the first to describe the heart as a muscle and an organ with four cavities, and to explain blood circulation, the two auricles contracting and the two ventricles relaxing simultaneously (and vice versa). Leonardo da Vinci, a bright anatomist, allied his superb capacity of observation to his unique skill for drawing. Leonardo da Vinci, being a dedicated observer of the nature, has produced the so-called Codex of Leicester, a manuscript with 72 pages written in 1504–1508, that shows diagrams focused on water and its dynamics (river floods, dams, and fossils) based on observations of the river Arno that crosses the town of Florence.

As a dissector, Andreas Vesalius (1514–1564), a professor of anatomy at the University of Padova in the book *De humani corporis fabrica libri septem* published in 1543, reprinted in 1556, details and systematizes the anatomy of the human body, producing more than 200 illustrations grouped in three categories: skeleton, muscles, and individual parts of the body.

Philippus Aureolus Theophrastus Bombastus von Hohenheim, better known as Paracelsus (1493–1541), a physician and alchemist born in the village of Einsiedeln, Switzerland, who studied medicine in Ferrara, first formulated drugs based on substances extracted from minerals through chemical reactions and created a branch of chemistry called *iatrochemistry*, which preceded the current pharmacology, aiming at the study and use of chemical substances for therapeutic purposes.

Iatrochemistry was a medical doctrine according to which the human organism was able to establish a set of chemical equilibria. According to this theory, the disease resulted from a chemical imbalance and health was the condition of equilibrium.

Paracelsus (1493–1541), a physician and surgeon, being considered the father of *pharmacology* said that “All substances are poisons, there is none that is not poison. The right dose differentiates the poison from the remedy.” This phrase expresses well the idea of medical geology, whose objective is to search for the correct balance of the incorporation of *minerals/chemical elements* with a view to the improvement and maintenance of human health. Paracelsus used the term “terra sigillata” for the first time to describe a clay from Malta, a clay named *terra Malitea* (*In*: Spalek and Spielvogel 2019). These same authors mention that Bernard Palissy (1510–1589), a French potter, geologist, and natural historian, attempted to explain the action of “terra sigillata Lemnia” in his work entitled “Discours Admirables” from 1580, concluding that this type of clay may also be present in other parts of the world, an assumption which was later proven correct. Effectively, clays similar to those from the Greek islands have been discovered in various countries: Spain (*terra Hispanica*), Portugal (*terra Portugallica*), Italy (*terra Florentina*), Turkey (*terra Turcica*), Armenia (*terra Armenica*), and Silesia (*terra Silesiaca*). Clay torches of these clays after being properly stamped in similar manner to Greek *terra sigillata* were then commercialized, and only in the second half of the eighteenth century the medicinal use of these clays was discontinued. In Silesia, in Central Europe, the famed *terra Silesiaca* was indicated for the treatment of wounds caused by the bites of dogs infected with rabies, wounds bleeding, intestinal disorders, etc. Oral treatment in humans used clay mixed with wine or beer, whereas treatment in animals used clay mixed with vinegar and ash (*In*: Spalek and Spielvogel 2019). In 1618, *terra Silesiaca* was first named in the Pharmacopoeia Londinensis alongside the classic clays from the Mediterranean region. Collections of stamped clay troches of *terra Silesiaca* can be seen in regional museums, for instance, in Wroclaw and Heidelberg.

Alchemy included metallurgy, so Paracelsus became interested in mining and visited several mines. In the publication *Chronica und Ursprung dises lants Kernten* (1538), Paracelsus described the laboratories associated with some mines and, as a doctor, he observed how the fumes, dust, and ash existing in the mines or produced in the process of smelting of the ores affected the health of the miners and other workers. Unfortunately, Paracelsus observations effectively in the field of medical geology were only published after his death in 1567 and in 1589–1591. There were risks to health related to underground mining work and to the surface preparation and ore concentration, risks manifested in respiratory diseases, but also with the mercury poisoning that the alchemists admitted to participate in the composition of the whole matter.

Georg Bauer (1494–1555) better known in Latin by the name Georgius Agricola, in his book *De Re Metallica* published in Latin, in 1556, of which the first English translation in 1912 was due to Herbert Hoover, a mining engineer who later was president of the USA, and to his wife Lou Henry Hoover, a geologist and Latinist. The book that has remained as the authoritative text on mining for about 180 years after its publication reports on the use of *medicinal clay* and states that certain minerals, either in the solid state or after dissolution, may have either curative effects, or act as poisons.

Georg Bauer, a German physician, humanist, and scholar, became interested in the theoretical and practical aspects of mining, metallurgy, and geology after being appointed town doctor of Joachimsthal (now Jáchymov), a silver-mining community on the east side of the Erzgebirge Mountains or Ore Mountains in what is now the Czech Republic. In *De Re Metallica*, he mentions the harmful effects on the health of the miners, in effect causing respiratory difficulties, the powders produced particularly when the mining was done by dry means, as it happened in the mounts of the Carpathian Mountains. For Georg Bauer, notwithstanding the health risks, without metals no other activities, such as architecture or agriculture, are possible. Also, for him, metals have been placed underground by God, and man is right to extract them and use them.

Already during the Middle Ages, but even more so in the Renaissance, some minerals were used as poisons of mineral origin for criminal purposes. The best known were *arsenic* salts, As_2S_3 and AsS which had the advantage of having no odor and taste and could be used without the victim’s awareness. In the history, there is a good example of specialists in poisonings using soluble salts of *arsenic* (As), as is the case of the Borgia family in Italy in the fifteenth century. Later, in France, in the seventeenth century, Catherine de Médicis introduced the modality of the use of poisons incorporated in perfumes. Also, Andrea Bacci in his book *De Thermis* (1571) recommended the use of *fango* (thermal mud) in the treatment of rheumatic pathologies, ulcers, and edemas.

At the height of the Renaissance, the discoveries by the Portuguese and the Spanish in the fourteenth and fifteenth centuries made an important contribution to the development of medicine because they provided the meeting of peoples and cultures very diverse and promoted the sharing of experiences and the exchange of knowledge in a new framework that has been designated as a “first globalization” (Cardoso 2017a, b).

The Portuguese mathematician Pedro Nunes (1502–1578), although not involved in sea voyages, created a new branch of applied mathematics called *mathematics of navigation* and developed the “nónio,” an instrument of measurement used in astronomy. Pedro Nunes, who was the cosmographer of the Kingdom of Portugal, believed that scientific knowledge should be disseminated and shared. The sharing of experiences and the collection of information on plants, particularly of vegetable origin, was the work of, among others, explorers, missionaries, and physicians.

In the sixteenth century, the physician most knowledgeable of the therapeutic use of medicinal plants in Spanish America was Nicolás Monardes (1493–1588), a professor of medicine at the University of Seville. Also, the Portuguese physician and botanist Garcia de Orta (1499–1567), a native of Castelo de Vide, used medicinal plants, minerals, and “mezinhas” or drugs to treat patients, first in Castelo de Vide, then in Lisbon, and later in Goa where he was engaged in the fight against the cholera epidemic that plagued Goa in 1543. In 1563, he published the book *Coloquios dos Simples e Drogas he Cousas Mediçinais da Índia* or *Colloquies of Simple and Drugs and Medicinal Matters of India*, a pioneering book on tropical diseases and also on diseases whose cure could be obtained by the use of plants, minerals, and drugs. Also, yet, according to Cardoso (2017a, b), the physician Aleixo de Abreu (1568–1630), who practiced in Angola and Brazil, in his work “Treaty of the Seven Diseases” describes, in particular, the diseases *scurvy* (that affected navigators) and *malaria* (typical tropical disease). The quinine-based medicines that the Indians used to combat malaria were spread throughout Europe by missionaries, mainly Jesuits. Such medicines, with emphasis on the famous *water of England*, were in the seventeenth and eighteenth centuries the most effective in the fight against malaria.

Also, during the Renaissance the first texts of the so-called pharmacopoeias, namely, the “Pharmacopoeia of Valence” (1601) were produced and “Pharmacopoeia Londinensis” (1618), which contained the drugs used in the production of medicines, and were classified, mentioned, and referred to the modes of use of several minerals used for medicinal purposes.

During the eighteenth, nineteenth, and twentieth centuries clay-based materials were used for therapeutic purposes, the so-called curative mud for mud therapy and later the so-called healing peloid for pelotherapy in the form of baths and poultices, were profusely used in European spa resorts, particularly in France, Germany, and Italy. For example, in France, Dax, Balaruc, and Aix-les-Bains Resorts have been and still are famous and are representative of the use of healing mud/peloid for medicinal purposes, in particular for rheumatic conditions.

In Portugal, the first pharmacopoeias appeared only in the eighteenth century written by apothecaries of religious orders. This is the case of the “Pharmacopea Lusitana,” a pioneering work in Portugal by the canon and apothecary Frei D. Caetano de Santo António of the Order of St. Augustine, whose first edition with 431 pages dates back to 1704; two subsequent editions are dated of 1711 and 1725. In “Pharmacopea Lusitana,” a *medicine is identified* as being “One who can alter our nature,” or as being “One who is applied to a human body and will heal its infirmities," or as "That instrument which doctors use to heal our infirmities," and the medicines were of two types: "simple or natural" and "composed of one or more things together by art." The first "Official Portuguese Pharmacopoeia," the "General Pharmacopoeia," by the physician Francisco Tavares, was published in 1794, and until now several official editions have been published, the latter complying with European Community Standards, because Portugal subscribed in the 80s decade the convention that led to the elaboration of the "European Pharmacopoeia." In Portugal, the current edition of the pharmacopoeia is the "Portuguese Pharmacopoeia IX." There is also an International Pharmacopoeia edited by the WHO (World Health Organization) prepared by a committee of experts from several countries, written in English, French, and Spanish. According to Pita (1999), the work of Francisco Tavares for about 40 years served as a standard to medical prescription, pharmacy teaching, and drug production. In the "General Pharmacopoeia," there are preparations using the metals *antimony* (Sb), *lead* (Pb), *iron* (Fe), *mercury* (Hg), *silver* (Ag), and *zinc* (Zn).

The Portuguese pharmacy of the seventeenth and eighteenth centuries had been strongly marked by the so-called monastic or conventual remedies, and several monastic pharmacists produced medicinal products and pharmaceutical texts (Oliveira 2011; Pita and Pereira 2012).

In the book entitled *Materia Medica Physico-Historico-Mechanica, Reyno Mineral* published in London in 1758, the Portuguese physician Jacob de Castro Sarmento (1691–1762) persecuted by the Inquisition and exiled in London, exposed his growing discredit regarding the long established myths about the therapeutic effects of some mineral gems (e.g., the effect of ground *magnetite* ingested by parturient women was strongly discredited and inadvisable). On the contrary, the beneficial effects of Baltic *amber* were emphasized in treatments of diseases, for example, of the skin, the methods developed for the preparation of powder, oil, and dyeing from the amber being described.

Until the eighteenth century, natural history and medicine went hand in hand. According to the alchemist doctor Oswald Croll (1563–1609), a follower of Paracelsus, the "Earth is the Pharmacy of God," being the natural world, represented by animals, vegetables, and minerals, the repository of the remedies.

At the end of the eighteenth century with the revolution of chemistry due to Antoine Lavoisier (1743–1794), this founder of chemistry published the *Elemental Treaty of Chemistry* in 1789, a work that placed chemistry on par with physics as a quantitative science, distancing it definitively from alchemy. Lavoisier identified the oxygen by noting that it, when in contact with flammable substances, produces combustion, and classified water as a substance composed of oxygen and hydrogen, whereas until then water was considered a simple substance, that is, impossible to compose. In Lavoisier's book, he formulated the "Principle of the Conservation of Matter," also known as "Lavoisier's Law," expressed as "Rien ne perdir, rien ne se creé, tout se transformaforme" or "In a chemical reaction the total mass of the matter involved is the same in the end as it was in the beginning."

Lavoisier pioneered the so-called stoichiometry. So chemistry went into drug preparation. Various salts such as *Salt de Rochelle* or *Seignette salt*, *salt of Glauber*, *salt of Seidlitz* or *Salt Epsom*, and *salt of Prunella*, among others, participated in this preparation. The *salt of Rochelle* or *Seignette*, $KNaC_4H_4O_6.4H_2O$, i.e., sodium and potassium tartrate, which was discovered in 1675 by apothecary Pierre Seignette in La Rochelle, France, has laxative functions. *Glauber's salt*, $Na_2SO_4.10H_2O$, corresponding to the mineral *mirabilite*, was first identified by the chemist and German apothecary Johann Glauber (1604–1670) in a hot spring in Austria was known as *mirabilis salt* (miracle salt) because of its medicinal properties of a laxative nature. *Epsom salt*, $MgSO_4.7H_2O$, corresponding to the mineral *epsomite*, was first discovered in the solid residue of one hot spring water that emerges near Epsom, has laxative and bronchodilator functions, the latter being important in the treatment of asthmatic patients. *Glaser's Prunella salt* is potassium nitrate, KNO_3.

In Portugal, the interest in science resurfaced in the eighteenth century with King D. José I (1689–1750) who sponsored the very important Pombaline Reform of the University of Coimbra, which began in 1772 by José Sebastião de Carvalho e Melo, better known as Marquis of Pombal, who quickly and technically effective directed the reconstruction of Lisbon after the great and highly destructive earthquake of 1755. Very influential in the reform process were some of the so-called outsiders like the Jewish doctors António Nunes Ribeiro Sanches and Jacob de Castro Sarmento and the physicist João Jacinto Magalhães.

The concept of public health, that is, the art and science whose object is the protection of the health of the populations, gains affirmation in the eighteenth century, particularly through the studies of British physicians, chemists, geologists, and mineralogists, such as William Cullen (1710–1790), Joseph Black (1728–1799), and John Walker (1731–1803) who, further emphasizing the therapeutic properties of minerals and thermal waters, rather than health protection, have laid the foundations for future generations of physicians who were confronted with the necessary control of health threats resulting from rapid industrialization and urbanization in the early nineteenth century.

From the most influential people in this period, Dr. Alexander Parkes (1819–1876), the first professor of military hygiene and author of a pioneering book on public health published in 1864, discussed the geological influences on health (Bergman 2013, *In*: Duffin et al. 2013). Parkes demonstrated how geological factors could pose a health risk. In 1859, in London, the book *On the Origin of Species by Means of Natural Selection* was published by the English naturalist Charles Darwin (1809–1882), where the theory of the "Evolution of Species" was defended by natural selection that came to be proven with the progress of knowledge in the fields of microbiology and genetics. All species, both animal and plant, descend from a common ancestor. The characteristics of each species are transmitted to the following generations, and intergenerational differences can arise due to small mutations, whose accumulation over time leads to the appearance of new species. Some species survive because of their good adaptation to the environment, while others cannot and are extinct.

Natural environment mainly through geology, geography, and climate decisively contribute to species evolution. The metaphor of the "Tree of Life" adequately describes the succession and coexistence of species over time. Fossils are consistent testimony to the evolution of species. The so-called laws of heredity developed by the Czech botanist Gregor Mendel (1822–1884) and the DNA, the code of life, developed in the twentieth century, provided consistent scientific evidence of Darwin's theory.

In Portugal, in the nineteenth century the Portuguese-Brazilian naturalist José Bonifácio d'Andrada e Silva (1763–1838) pioneered mineralogy (minerals science) with much research done in Brazil and in Portugal was a disciple of both the French monk René Haüy (1743–1822), and was also a naturalist and considered a pioneer of crystallography studies, as was the German Abraham Gottlob Werner (1749–1817), considered the founder of modern mineralogy and who established the first systematic of minerals. The theory of crystal structure based on the so-called Haüy polyhedral units was later updated and replaced by the crystal lattice theory attributed to the French physicist Auguste Bravais (1811–1863). Indeed, the crystals are tridimensional and triperiodic networks that many years later could be confirmed and observed under the high-resolution electron microscope.

In Portugal, the botanist Felix Avelar Brotero (1744–1828), who studied the national flora, published two notable works, *Flora Lusitania* (1804) and *Phytographia Lusitaniae selectior* (1816–1827), which developed the Botanical Garden of Coimbra and, at the end of the century, the world-renowned mathematician in his time Francisco Gomes Teixeira (1744–1828) who became the first rector of the University of Porto.

The so-called Pharmaceutical Revolution arises when drugs based on natural products give rise to highly complex chemical substances occurred in the early nineteenth century with the discovery and isolation of active substances in certain plant species. *Narcotine*, *morphine*, *cinchonine*, *caffeine*, *strychnine*, *brucine*, and *quinine* were the first glycosides and alkaloids to be discovered and isolated. Gradually this list was increased with *codeine*, *cocaine*, *ephedrine*, *atropine*, and *papaverine*. Later, all these products were produced synthetically, in more pure and controllable forms.

The industrialization of medicines was another stage in the pharmaceutical evolution. The first pharmaceutical specialties appeared in the nineteenth century. The "Pharmaceutical Revolution" was part of the wider "Industrial Revolution" that succeeded the "Second Scientific Revolution" which really began in England in the 1760s. Handicraft production methods have given way to production methods using machines.

Four periods are considered in the "Industrial Revolution":

1. Between 1760 and 1840, represented by the discovery of *coal* as a source of energy for the operation of steam engines and locomotives.
2. From 1840 to the middle of the twentieth century, represented by the discovery and use of *electricity*.
3. From 1960 to the end of the twentieth century, represented by the advent of information technology, personal computers, Internet, and digital platforms.
4. Beginning already in the twenty-first century, it is represented by the so-called Industry 4.0 characterized by the automation of processes, the use of robots, 3D

printers, the development of renewable and environmentally friendly forms of energy, and the wide use of artificial intelligence.

The microbial cause of disease arises with the advances in *microbiology* pioneered by Louis Pasteur (1822–1895) who discredited the theory of spontaneous generation by identifying pathogens that developed diseases such as *cholera*, *rabies*, and *anthrax*. Also, Robert Koch (1843–1910), known for the discovery of the *tuberculosis bacillus* (which in 1943 was effectively combated with the antibiotic called streptomycin), discovered the *vibrio of cholera* and the *anthrax bacillus*. Effectively, the diseases hitherto regarded as inflammations or fevers were of bacterial origin.

Created the bases for vaccination, many of the diseases dangerous to humans and other animals were being eliminated. *Vaccines* are based on the principle of giving the immune system the ability to develop weapons – *antibodies* – against bacteria and viruses. The *vaccines* employ either the disease-causing microorganism in an attenuated form prior to the injection or the chemically inactivated microorganism. Later, *vaccine* production resorted to genetic engineering techniques using only pieces of disease-causing agents; another approach is to use viruses to kill viruses. *Mercury*, though in minute quantities, enters some vaccines.

The idea of combating bacteria with drugs arose when the Scottish bacteriologist Alexander Fleming in 1928 discovered the fungus *Penicillium* capable of killing certain types of bacteria. This was the first step in the development of antibiotics; penicillin was considered the "miracle drug" of the twentieth century, beginning in the 1940s, the golden age of antibiotics.

The hope for cure of *syphilis* (an infectious and highly contagious venereal disease that plagued mankind since the late fifteenth century) related with homosexual practices, particularly in men involved in wars, as was the case most recently in World War I, resulted from studies carried out by the German chemist Paul Ehrlich and the Japanese bacteriologist Sahachiro Hata who discovered and isolated a new *arsenic* compound (As), which they called "arsphenamine" and is the active molecule of the drug salvarsan which proved to be effective. Initially, in the sixteenth century, the attempt to cure *syphilis* went through the use, among other natural products, of *mercury* (Hg) ointments.

Dysentery was also a common illness in soldiers on the fronts of war, World Wars I and II. In World War I, the mineral clay mixed in the mustard proved to be an effective medicine (*In*: Rautureau et al. 2010, p. 12). On the contrary, still in war fronts, a negative effect of clay was cited by Cross (1919, p. 175). The renowned geologist Charles Whitman Cross (1854–1949) who develop research focused on the relationships of geology and health reported a health problem that afflicted troops in particular areas of Europe during World War I. In some places, the troops at the front engaged in tunneling and trenching became incapacitated by the formation of skin wounds that rendered them susceptible to infections. The medical corps could not understand the prevalence of this trouble in restricted areas. The clay material of the tunnel walls was closely examined and found to act like *fuller's earth* clay in removing the natural greases from the skin. Later, *Ca-montmorillonite* had been identified as the main constituent of such clays and considered responsible for their specific sorption properties. Associated with this clay mineral *kaolinite*, *palygorskite*, *calcite*, *dolomite*, and *quartz* can occur too. *Fuller's earth* is the English name of a clay common in Surrey, England, and its name reflects its historic use for cleaning or fulling of wool by textile workers called "fullers." In the past centuries, fullers kneaded fuller's earth and water into woolen cloth to absorb oils and other greasy impurities as part of the cloth finishing process.

From the twentieth century onwards, the visualization of the interior of the human body has become possible facilitating the diagnosis of the causes of diseases, with the use of increasingly complex techniques, some of which involve minerals. Beginning with X-rays discovered accidentally in 1895 by the physicist Wilhelm Conrad Röntgen (1845–1923), this electromagnetic radiation of small wavelengths, and logically of high energies, was capable of penetrating matter. X-rays used in medicine are called "soft X-rays" because they can penetrate only the soft tissues of the body and allow the hard tissues to be visualized in the case of bones. In turn, X-rays used, for instance, in mineralogy are called "hard X-rays." X-rays were first used in a military context during the Balkan War (1912–1913) and especially from October 1914 by Marie Curie, Nobel Prize, revealing broken bones and bullets embedded in the bodies. X-rays were followed by ultrasounds used for the first time in 1942 for medical diagnosis and magnetic resonance, which was discovered in 1946.

Computed axial tomography (CAT) arises in 1967 and a decade later appears the positron emission tomography (PET) that requires an injection of short-lived radioisotopes that emit gamma rays and allows images with great detail.

The so-called nuclear medicine is a specialized area of medicine that uses radioactive substances, radioisotopes or radionuclides, to obtain an image of the human body, in view of the diagnosis and therapy of certain diseases, cancer in particular. Radionuclides emitting ionizing radiation are of artificial origin and are obtained by bombarding stable atoms with subatomic particles (neutrons, protons, etc.) causing nuclear reactions and converting stable nuclei into unstable (radioactive) nuclei. In such a bombardment, equipment such as nuclear reactors and particle accelerators (linear and cyclotron) are used.

The so-called imaging techniques used in nuclear medicine provide physicians with a new way of seeing inside the human body, combining the use of radioisotopes, detectors, and computers.

Among the mentioned techniques that use images to detect tumors, aneurysms, and various situations of inadequate functioning of organs and tissues, we can highlight positron emission tomography (PET), single photon emission computed tomography (SPECT), cardiovascular imaging, and bone imaging. In the PET technique, a noninvasive diagnostic imaging technique with no pharmacodynamic effects, the most used positron-emitting radioisotopes or radiolabels are ^{18}F and ^{11}C characterized by reduced half-life. In the SPECT technique using radiation emitter Υ (gamma), the most commonly used radionuclides are ^{123}I, ^{67}Ga, and ^{201}Tl.

Certain bodies concentrate certain types of chemicals. In the case of the thyroid gland, this concentrates iodine whereby, using radioactive iodine ^{131}I, certain cancers of the thyroid can be detected and then treated. Also, certain cancers concentrate phosphates whereby injecting the ^{32}P isotope into the bloodstream can detect the tumors by their increased radioactivity. There are several radioisotopes used in nuclear medicine, all having rapid decays, from minutes to hours, and are eliminated in the urine and feces. The drugs that drive the radioisotopes to the affected organs or tissues are called radiopharmaceuticals (Sánchez 2001; Oliveira et al. 2006; Chain and Illanes 2015).

The radiopharmaceutical is a substance with a known biological affinity whose molecule has at least one radioactive atom (radioisotope or radionuclide) produced according to the norms recommended by ANVISA (National Agency of Sanitary Surveillance) and CNEN (National Commission of Nuclear Energy) and which is used for the diagnosis and treatment of various diseases, including cancer. It can be used by several routes, the intravenous being the most used. In the field of conventional nuclear medicine, the best-known diagnostic applications are *bone scintigraphy*, *myocardial scintigraphy*, *renal scintigraphy*, and *vesicourethral scintigraphy.*

The current century may remain for history as the century of *biomedicine*, science of interface between biology and medicine; of *astrobiology*, interface science between astrology and biology, having as main objective the identification of the origin of life; of *biotechnology*, interface science between biology and engineering; and of course of *environmental medicine*, science of the effects of the environment on health and its minimization if they are adverse; and of *environmental epidemiology*, science of the effects between environmental exposure and the prevalence and incidence of diseases, depending on variables such as genetics, age, lifestyle, occupation, etc. In the latter two areas referred to, certain knowledge and research results in the area of medical geology may play a role relevant and determinant.

According to Olden and White (2005), in the last 25 years, there have been impressive advances in biological and social sciences. The increasing concern of modern societies with the interactions between environment – in particular the geological processes and products – and health justified the emergence in the last two decades of the scientific field called *medical geology*, mainly focused on the negative effects of minerals and natural chemical elements, despite of their fundamental and paramount importance for both good health and living quality.

The fundamental target of medical geology is to show and demonstrate to the general public and to policy makers in particular, through examples with impact on public health and its good publicity in the mass media, the importance of medical geology.

The book entitled "*Essentials of Medical Geology: Impacts of the Natural Environment on Public Health*", Selinus O, Alloway B, Centeno J, Finkelman R, Fuge R, Lindh U, Smedley P (editors), first edition in 2005, and second edition in 2013, provide an excellent approach to the positive and negative impacts of minerals *latu* sensu *or* minerals *l.s.* on human health. The developments on geochemistry particularly raised on the last 25 years significantly had contributed to the development of medical geology.

Today, we well know that the excessive exposure to certain minerals can cause chronic and eventually lethal diseases, such as *silicosis*, *asbestosis*, *talcosis*, *siderosis*, *baritosis*, *manganism*, and *podoconiosis*. Also, both deficiency and excess of certain trace elements can cause chronic and acute poisoning and diseases, such as *arsenicosis* (due to arsenic), *antimoniosis* (due to antimonium), *saturnism* (due to lead), *selenosis* (due to selenium), *mercurosis* (due to mercury), *cadmiosis* (due to cadmium), *fluorosis* (due to fluoride), and *thallotoxicosis* (due to thallium).

The following publications on the subject "medical geology" should be also referred to: Bunnell et al. (2007), Gomes and Silva (2007), Selinus et al. (2010), Davenhall (2012), Centeno et al. (2016), and Finkelman (2019).

Other important target of *medical geology* is to raise awareness and prepare researchers for a field of knowledge that is so strongly interdisciplinary, that it should interest and involve people with professional training in diverse scientific areas, such as *medicine*, *geology*, *biology*, *biochemistry*, *biophysics*, *mineralogy*, *geochemistry*, *hydrogeology*, *hydrochemistry*, *ecology*, *environment*, *food chemistry*, *nutrition*, *toxicology*, *pathology*, *epidemiology*, *etiology*, *territory planning*, and *economics*.

Modern *public health* practice requires multidisciplinary teams of *public health* workers and professionals. Teams might include epidemiologists, biostatisticians, medical assistants, public health nurses, midwives, or medical microbiologists. Depending on the need, environmental health officers or public health inspectors, bioethicists, geochemists, toxicologists, and even veterinarians might be called on.

Minerals are essential to life and living quality, but in specific situations *minerals* can put human health at risk. Naturally the *concept of mineral* in the field of earth sciences has changed along the times following the developments in science and technology, firstly based on physical properties, then on chemical properties, later yet on physical-chemical properties, and still later on crystallochemical properties, taking advantage of X-ray diffraction, electron diffraction, and X-ray fluorescence techniques and applications.

Mineral *latu sensu* or mineral *l.s.* can occur in the whole natural environment in three main forms as follows:

1. In rocks and soils, both in the form of *mineral itself*, that is, as natural, inorganic, and crystalline solid, expressed in Latin asmineral *strictu sensu* or mineral *s.s.*, and in the *elemental free form* (chemical element of natural origin constituting the *minerals s.s.*, and which in the natural environment occur solvated or fixed to inorganic and organic compounds);
2. In water, dispersed in the form of *mineral itself* (*mineral s.s.*) and/or in solution in the *elemental ionic form*;
3. In air, dispersed in the form of *mineral itself* (*mineral s.s.*) in suspended dust of natural and anthropogenic origin, and/or in the *elemental form* free or fixed in aerosols.

The concept of mineral *latu sensu* or mineral *l.s.* encompasses the concept of *mineral strictu* sensu *(mineral s.s.)* or *mineral itself* (natural, inorganic, solid, and crystalline product), adopted as so, for instance, in earth sciences, soil sciences, and materials science, as well as the concept of *mineral* (chemical element of natural and inorganic origin), adopted as so, for instance, in medical, pharmaceutical, and nutritional sciences. All the chemical elements of natural origin shown in the periodic table can be constituents of both *minerals strictu* sensu *(minerals s.s.)* and humans.

Very close relationships are known between *minerals strictu* sensu *(minerals s.s.)* and humans. Both are chemical systems built with the same fundamental blocks – the natural chemical elements – although in different concentrations. Both follow processes of formation, growth, and durability (sooner or later they disappear, since they are imperfect natural beings, characterized by inherited and acquired defects and disorders). In humans, such defects and disorders could be herein expressed as diseases of more or less gravity. In minerals, defects and disorders mean physical and chemical instability leading to alteration and disappearance.

We well know that the names of some natural inorganic and crystalline solids and of some natural elements sometimes coincide, as are the cases, for instance, of *gold* (Au), *silver* (Ag), *copper* (Cu), *iron* (Fe), *sulfur* (S), and *carbon* (C), the so-called native element minerals, most of these elements being classified as *metals*, which are fundamental constituents of *metalloproteins* and *metalloenzymes*. Also, it is well known that minerals participate in the constitution of all living beings and condition the quality of the natural systems that are life support: *soil*, *water*, and *atmosphere*.

In humans, minerals play three main roles:

1. Provide structuring in the formation of bones and teeth;
2. Help the maintenance of normal heart rate, muscle contraction and conduction of the nervous system, and acid/base balance;
3. Regulate cellular metabolism by being part of enzymes and hormones that control cellular activity.

There is much general and specific information on:

1st – The historical evolution of the use and effects, positive and negative, of *minerals l.s* on human health;
2nd – The sources (food, water, and air) and pathways (ingestion, inhalation, and dermal absorption) that rule the uptake or incorporation of *minerals* in the human body;
3rd – The functions of *minerals* in terms of health.

All natural and inorganic chemical elements or minerals are present in the human body, and a significant number of them are reckoned as essential to human health and classified as major, minor, and trace elements. Such elements could be good, tolerable, or toxic for health depending on the individual dose.

There is much information about the use of some minerals in pharmaceuticals and cosmetics as *active substances* and as *excipients*, their functions and applications being dependent upon mineral specific crystallochemical properties. Within such information, the one due to the authors Novelli (1996, 1998), Carretero and Pozo (2007, 2009, 2010), Viseras et al. (2007), Viseras and López-Galindo (1999, 2000), López-Galindo and Viseras (2004), López-Galindo et al. (2011), Glick et al. (2013), and Awad et al. (2017) deserves to be enlightened.

As *active substances* in pharmaceuticals, minerals can perform important specific functions, such as *gastric antacids*, *gastrointestinal protectors*, *antidiarroeics*, *laxatives*, *antianemics*, *antiseptics* and *disinfectants*, *dermatological protectors*, *sunscreen protectors*, *cosmetics*, *abrasives* and *mitigators of dental sensitivity*, *ocular congestion relievers*, *mineral supplements*, *means of diagnosis and treatment*, *immobilizers in orthopedics* and *molds in odontology*, *contrasting means in diagnosis*, and *hemostatic agents*.

In turn, as *excipients* in pharmaceuticals, minerals play the following main functions:

1. Improvement of organoleptic properties (taste, color, odor);
2. Improvement of physicochemical properties (viscosity, dispersibility, suspendability, and thickness);
3. Facilitation of preparation and conservation of formulations (utilizing dilution, lubrication, and drying);
4. Facilitation of release of the active drug ingredient in a particular site inside the organism.

Also, as *excipients*, minerals perform important specific functions, such as lubricants, taste correctors, disintegrators, diluents, binders or agglomerators, pigments, emulsifiers and thickeners, and carriers for the controlled release of drugs.

Today, we know that minerals as well as the *human body* are chemical systems that have in common many of their elemental constituents – the natural chemical elements. Therefore, the development of pharmacology has been parallel to the development of chemistry and also to the development of therapeutics that competes with medicine. Evolution has been so remarkable that presently in many pharmaceutical formulations minerals as natural products have been replaced by the so-called synthetic analogs produced in laboratories and industries even though with origin from natural products but having improved properties, for example, the purity grade. Of course, the participation of the minerals in the pharmaceutical formulations requires that they be submitted to previous industrial and laboratory processes used in the so-called pharmaceutical technology.

Minerals are utilized in *cosmetics*. In the manufacture of cosmetics, thousands of chemicals can be used. A typical cosmetic product contains anything from 15 to 50 ingredients. Most *cosmetics* contain a combination of at least the following ingredients: *water*, *emulsifier*, *preservative*, *thickener*, *emollient*, *pigment*, *fragrance*, and *pH stabilizer*. Some minerals can be incorporated in various cosmetic products, such as *sunscreens*, *toothpastes*, *creams*, *powders*, bathroom salts, and deodorants (Carretero and Pozo 2010). *Sunscreens* are widely used to protect the skin from the harmful effects of sunrays on exposure. *Zinc oxide* (ZnO) that corresponds to the mineral *zincite*, and *titanium dioxide* (TiO_2), corresponding to mineral polymorphs *anatase* and *rutile*, are the most effective approved mineral-based ingredients which protect the skin from sun damage. The synthetic analogs forms, particularly of TiO_2 minerals provide a good barrier on the skin able to reflect UVA and UVB rays avoiding their penetration down to the deep layers of the skin.

Some minerals, such as *calcite*, $CaCO_3$, and *niter*, KNO_3, are currently incorporated in *toothpastes* for two purposes: as abrasive or polishing agents; agents to diminish teeth sensitivity. Minerals containing potassium and nontoxic anions and being highly soluble in water, well exemplified by the mineral *niter* (KNO_3), are used in toothpaste formulations good for sensitive teeth; K^+ ions act on nerve endings inside dentine inhibiting the transmission of painful stimuli (Orchardson and Gillam 2000; Wara-Aswapati et al. 2005). Such formulations due to their both pharmaceutical and cosmetic characters could be classified as *cosmeceuticals*. *Calcite* ($CaCO_3$) is other mineral currently incorporated in toothpaste as abrasive/polishing agent due to the following two properties: *high whiteness* and *low abrasivity* (hardness of 3 in the Mohs's scale) comparatively to tooth enamel hardness (5 in the Mohs's scale).

Creams, *powders*, and *emulsions* containing some specific minerals are applied to external parts of the body in order to embellish or modify their physical appearance or to preserve the physicochemical conditions of the skin. Some minerals, such as *halite* (NaCl), *sylvite* (KCl), *epsomite* ($MgSO_4.7H_2O$), and *mirabilite* ($Na_2SO_4.10H_2O$), are used in bathroom salts due to their specific chemical composition and particularly to their high solubility in water.

Nanoparticles of different nature can be incorporated into *lipstick* and *lip gloss* in order to soften or smoothen the lips by preventing transepidermal water loss.

Pigments exhibiting wide range of colors were made from *gold* (Au) or *silver* (Ag) *nanoparticles* by mixing them in various compositional ratios and whose color can be maintained for a long period of time; *silica* nanoparticles used in lipsticks improve the homogeneous distribution of pigments, and once applied they prevent the pigments from migrating or bleeding into the fine line of lips.

Concerning the so-called special clays, besides their biomedical interest, clays have been a subject of man's interest owing to their easy availability in nature, to their cheap costs, and to the wide range of applications. With the progressive evolution of the knowledge acquired the man came to know that the medicinal earth is a geological material to which was given the name of clay.

Certain types of clay, which in the twentieth century were recognized for specific medicinal properties and functions, and to which scientific and commercial names were attributed, as well as other pharmacological preparations based on minerals, have since then become part of the pharmacopoeias (of the first that emerged in the sixteenth century to the contemporary ones), all as *active substances* or as *excipients*, in one case and another with different functions (Carretero and Pozo (2009, 2010).

The so-called nanominerals, clay minerals included, also play important functions in the field of *nanomedicine* defined as the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body. It embraces five main sub-disciplines which are in many ways overlapping and are underpinned by common technical issues: *nanomaterials and devices*, *analytical and imaging tools*, *novel therapeutics and drug delivery systems*, *clinical applications*, and *safety and toxicological issues* (environmental, manufacturing, and clinical use) (ESF-European Medical Research Council report, 2004). *Nanominerals* such as *carbon nanotubes*, *halloysite nanotubes*, *allophane* and *imogolite nanospherules*, and *tubules* have been thoroughly investigated having in mind their potentialities as drug delivery systems.

As a rule, the therapeutic activity of minerals takes place orally and topically. Orally, the following functions are highlighted: gastric antacid, gastrointestinal protection, antidiarrheal, antianemic, laxative, homeostatic, and dietary supplementation. *Geophagy*, particularly through ingestion of the so-called edible clays, is a good example of the internal use of minerals for curative purposes. Topically, the following functions are highlighted: antiseptic, anti-inflammatory, disinfection, and dermal protection. *Mud therapy* and *pelotherapy* are good examples of the external use of curative minerals in the form of poultices, patches, and facial masks.

About *geophagy* and *edible clays*, as well as about *mud therapy* and *pelotherapy*, the publications by Gomes and Silva (2007), Carretero and Pozo (2007), Rautureau et al. (2010), Rautureau et al. (2017), Gomes et al. (2013), and Gomes (2018) provide an overview of the subjects referred to. Clays are one of the oldest earth materials used for healing purposes in traditional medicine, and they continue to be applied in modern life for the treatment of various topical and internal ailments.

Clays and clay minerals can be used *unmodified* (natural or synthetic) or *modified* (composites such as *clay-drug hybrids*, *organoclays*, and *clay-polymer hybrids*) (Ruiz-Hitzky et al. 2015; Viseras et al. 2019; Satish et al. 2019). Indeed, more attention is being directed towards understanding the interaction between active biomolecules and clay minerals, particularly with regard to medical science and health. There is increasing interest in the use of clay minerals as agents on which drugs can be adsorbed and then delivered to target sites in the body in a manner which allows for controlled release of the drug. This has potential to be extended to the delivery of genes and vaccines (Zhou and Keeling 2013).

One of the peculiar features of the use of clays for therapies is the wide spectrum of pathologies and aesthetic worries that are cured using them. Nonetheless, some properties of clays seem to be advisable for most of their use in *spa* and *aesthetic medicine* (for specific purposes, the clay must be properly chosen):

1. Softness and very small or tiny particle size, since the application of the clay paste, particularly as face mask, can otherwise be unpleasant.
2. Adequate rheological properties which are important in the preparation of plastic pastes of easy application and adherence to the skin, characteristics required for the treatment.
3. pH similar to that of the skin so as to avoid irritation or other dermatological problems.
4. High adsorption capacity – clays can eliminate grease excess and toxins from skin, and they are very effective against dermatological diseases such as boils, acne, ulcers, abscess, and seborrhea; an organic active principle can also be incorporated into the clay mineral before its application to the patient’s skin for therapeutic and cosmetic purposes.

5. High cation exchange capacity (CEC), enabling an exchange of nutrients (K^+, Na^+, Ca^{2+}, Mg^{2+}, or others) to take place while the clay mineral is in contact with the skin.
6. High heat-retention capacity (retentiveness) – as heat is also a therapeutic agent, clay paste is mostly applied hot to treat chronic rheumatic inflammations, sport traumatisms, and dermatological problems.
7. Possibility of hydration across the skin, for instance, after dramatic dehydration by sun exposure or burns.

In the biomedical field of applications, clays are used in pharmaceutics (both as active ingredients in the case of *drug carriers* and as *excipients*), in cosmetics (sunscreens and topical care), in biomaterials (scaffold, hydrogel, foam, and film), biosensors (electrochemical), and medical devices (patches, implants, and medical plastics). As active substances or active ingredients, to certain types of natural clay of green or blue colors that bear reduced chemical elements or chemical species such as Fe^{2+}, Cu^{2+} and Zn^{2+}, are being attributed bactericidal properties, and in the last decade the significant investigation being carried out has confirmed such properties relatively to various pathogenic bacteria, and has tried to identify the mechanism of the *microbicidal action*, and to establish the methodologies for both internal and external (topical) applications.

Clay bacteriostatic/bactericidal activity does not exist if clay is in the dry state; only when clay is in the hydrated state, for instance, in the paste or poultice state, the *microbicidal* action exists. Such *microbicidal* action creates high expectations when both public health and science are becoming more and more apprehensive and engaged relatively the increasing resistance of bacteria to antibiotics (Diekema et al. 2004; William Arias and Murray 2009; Williams and Haydel 2010; Otto and Haydel 2013; Morrison et al. 2016; Gomes et al. 2020).

Microbes are essential components of most environments on Earth, for instance, in geomaterials such as soils, clays, and mineral waters. Minerals provide microbes with nutrients, energy, and livelihood habitats, and microbes impact mineral weathering and diagenesis through their effects on mineral solubility. By contrast, microbes can form minerals as a by-product of either their surface reactivity towards soluble metals or as a consequence of their metabolism (Dong and Lu 2012).

The so-called microbiome is an essential component of the human body contributing to human health and disease. The importance of the interaction microbes/minerals has been reckoned particularly in the last decades, the so-called geomicrobiology became a very interesting field of research.

Other situations are known in which minerals play important roles with both positive and negative effects on human health, such as the so-called biominerals formed by the action of biological or cellular activity (Skinner 2000). The commas in the term “minerals” are justified because the true minerals are crystalline solids of inorganic origin formed in the natural environment without human intervention, while the *biominerals* being also crystalline solids analogous to the true minerals are produced in the human body through exclusively biological processes.

In human tissues, *biomineralization* may occur in two modes: *physiological* – essential for some physiological systems, such as bones and teeth; and *pathological* – causing certain pathologies, such as with the so-called stones or stones that occur in the kidneys and in other components of the urinary system and also in the gallbladder.

Relevant information regarding both physiological and pathological *biomineralization* is provided by several authors, such as Skinner (2000, 2005a, b), Elliot (2002), Dove (2010), Beniash (2011), Combes et al. (2016), Endo et al. (2018), and Demichelis et al. (2018). Also, regarding the so-called ectopic microcalcification, well exemplified by vascular calcification, coronary calcification, and mammary calcification, the following authors deserve particular reference: Varma et al. (2008), Pierre-Louis et al. (2009), Beer et al. (2010), Hajsadeghi et al. (2011), and Cottignoli et al. (2015a, b).

About 50 *biominerals* are already identified in living things. Most organisms produce mineralized tissues in which phosphates and carbonates of calcium and almost amorphous silica participate. *Calcite* and *aragonite* that form the shells of oysters and other mollusks are good examples of *biominerals*. Also, *magnetite* (Fe_3O_4 or $FeO.Fe_2O_3$) and *greigite* (Fe_3S_4) existing in the so-called magnetotactic bacteria are other examples of *biominerals*.

Magnetotactic bacteria are a group of Gram-negative bacteria capable of responding to magnetic fields due to the presence in the cytoplasm of nanoparticles of magnetic iron (under *magnetite* and *greigite* mineral species) surrounded by membrane, called *magnetosomes* (magnetic dipoles), responsible for orientation and migration of *magnetotactic bacteria* along the lines of the geomagnetic field (Blakemore 1975). Yan et al. (2012) review all information on *magnetotactic bacteria*, magnetosomes, and their applications. Recently, magnetosomes were used as drug carriers (Sun et al. 2011; Alphandéry 2014) and as contrast agents for MRI (Vermed et al. 2009).

Minerals equally play important and positive roles in the human body through the so-called biomaterials, in the form of metal alloys, special ceramics, and bioactive glasses. It is now possible to manufacture human tissues and organs using so-called tissue engineering and stem cells are essential raw materials for this purpose.

Mineral water is essential to life, to human body, and to human health. Experience has shown the existence of healing waters, and according to their specific physicochemical properties, they are used in the treatment of specific diseases. Concerning *mineral water*, there is a worrying concern about the increasing exposure of subterranean aquifers, whose mineral water can either be collected for human consumption or, perhaps, to be used in *thermalism*, due to chemical and microbiological contamination of anthropogenic origin, in spite of the existence of aquifers in which, for natural reasons, high concentrations of toxic chemical elements, metals and/or metalloids, may occur making improper the use of water for domestic consumption.

There are many scientific references on the subject "Mineral Water and Human Health." The book entitled *Drinking Water Minerals and Mineral Balance*, Rosborg I (editor), 2015, is an excellent overview of minerals, both macro-elements and micro-elements, in mineral water and their effects in humans, the current drinking water regulations being well focused and dealt with.

Thermalism is an important economic activity in many countries with reckoned effects on the health and well-being of users, being defined as “The use in Thermal Resorts or Thermal spas of natural mineral water (deep circulation water characterized by the stability of its chemical, physicochemical and microbiological properties) and other complementary means for the purpose of prevention, therapy, rehabilitation or wellness.” The so-called thermal medicine or health resort medicine, i.e., the use of *thermal mineral waters* for therapeutic purposes, is an important component of the *medical hydrology*, a scientific field that covers scientific/technical domains dealing with the medicinal use of water, methods of application, and solutions.

Thermalism includes *crenotherapy* which involves the use in thermal resorts or thermal spas of certain mineral waters considered medicinal products both for internal applications (ingestion and inhalation), and for topical applications (various baths and hydrotherapy). These waters which in general are of more or less underground deep circulation, called natural mineral waters and spring waters are differentiated, in terms of chemical composition (bicarbonate sodium, gasocarbonic, sulfated calcium, bicarbonate sodium sulfide, chlorinated, etc.), in terms of mineralization degree (hypersaline, mesosaline, hyposaline), and also in terms of temperature (*hot* in the so-called hot springs and *cold* at the emergence site).

There are many publications on the therapeutic use of water, natural mineral water in particular, within the scope of medical hydrology, some deserving to be enhanced, such as Maraver (2017), Carbajo and Maraver (2017, 2018), and Teixeira (2009, 2012, 2016, 2017).

Thalassotherapy is another important economic activity within the scope of medical hydrology that by definition is the “Use of seawater, sea products (sand, mud, salt, algae, and aerosols) and seaside climate as a form of therapy.” However, the actual definition of *thalassotherapy* is more precise considering “The combined use with preventive and therapeutic purposes of sea water and sea derived products, under counseling and medical supervision, inside the adequate facilities of establishments located nearby the sea.”

About *thalassotherapy*, the very recent papers by Morer (2016) and Gomes et al. (2019) report the historical foregoing, the concepts, the physical and chemical properties, and the application methods of seawater and of its derived products (mud, sand, algae, salt, and aerosols) for therapeutic purposes.

Human health benefits provided by *thalassotherapy* result from the minerals, either dissolved in seawater or participating in the chemical composition of sea-derived products: mud, sand, salt, and marine aerosol. The individual use for preventive and therapeutic purposes and under medical supervision of any of aforesaid sea products should not be called *thalassotherapy*, unless it takes place inside the facilities of a Thalasso Centre where the use of seawater is necessarily practiced too.

As a rule, seawater and their derived products (sand, mud, and salt) are therapeutically used in separate *thalassotherapy*, *psammotherapy*, *mud therapy/pelotherapy*, and *halotherapy* spas. Only exceptionally, seawater and its sand and mud products are used together in the same Thalasso Centre for therapeutic purposes (Gomes et al. 2019).

Thalassotherapy treatments are indicated mainly for diseases of the respiratory system (asthma, rhinitis, and sinusitis), for allergic skin diseases (eczema, acne, and psoriasis), and for rheumatic diseases and skeletal muscular diseases (arthrosis, arthritis, sciatica, and post-traumatic); treatments are contraindicated in the following cases: severe heart failure, very high hypertension, phlebitis, ulcerated or infected inflammatory dermal lesions, and neoplasias (Teixeira 2010).

Minerals can also have deleterious effects on humans. It is known that a good part of the human diseases is related to the minerals of either *geogenic* or *anthropogenic* origin present in the natural environment that serves as habitat for the man. It is effectively demonstrated that in the natural environment, man's exposure to certain geological materials and processes can be a cause of disease, some of which can be lethal. For example, excessive exposure to certain potentially toxic chemicals, such as arsenic, lead, cadmium, mercury, selenium, fluorine, uranium and radon, which may be present, either adsorbed to soil particles and being able to be utilized by plants which are at the base of the food chain, or in the water, or yet in the air.

On natural sources of airborne minerals, such as desert dusts, volcanic dusts, and volcanic gases, and health hazards, Posfái and Molnár (2000), Garret (2000), Buseck et al. (2000), Prospero (2001), Gieré and Vaughan (2013), Miller and Wark (2008), Williams-Jones and Rymer (2015), and Edmonds et al. (2018) are excellent references. Regarding the anthropogenic sources of airborne minerals and health hazards, Martin et al. (2014), van Thienen and Spee (2008), and Gbadebo and Bankole (2007) are excellent references too.

Minerals *s.s.* and certain industrial products derived from airborne minerals in the form of dust, particularly those that can be classified as *nanominerals* (clay minerals and non-clay minerals with particle size measured in nanometers, being 1 nm = 10^{-9} m), may cause serious problems in the respiratory system and in other organs by diffusion across the membranes.

There are people who have professional occupations involving the exploitation of mineral resources in mines and quarries; such people inhale mineral dust, which can result in serious pathologies of the respiratory system, such as *silicosis*, *asbestosis*, *berylliosis*, *siderosis*, *and talcosis* caused by *crystalline silica*, *asbestos*, *beryl*, *iron oxides (hematite and magnetite)*, and *talc*, respectively, which can be lethal, particularly if the exposure is intensive and long-lasting.

References

Agricola G (1950) De Re Metallica (1556), translated by Hoover H and Hoover LH. Dover Publications, New York

Alphandéry E (2014) Applications of magnetosomes synthesized by magnetotactic bacteria in medicine. Front Bioeng Biotechnol. https://doi.org/10.3389/fbioe.2014.00005

Arias CA, Murray BE (2009) Antibiotic-resistant bugs in the 21st century: a clinical super-challenge. New Engl J Med 360:439–443

Awad ME, López-Galindo A, Setti M, El-Rahmany MM, Viseras C (2017) Kaolinite in pharmaceutics and biomedicine. Int J Pharm 533:34–48

Aziz N, Gilani AH, Rindh MA (2002) Kushta (s): unique herbo-mineral preparation used in South Asian traditional medicine. MedHypotheses 59(4):468–472

Barroso MS (2013) Bezoar stones, magic, science and art. In: Duffin CJ, RTJ M, Gardner-Thorpe C (eds) A history of geology and medicine. Geological Society, London. Special Publication n° 375, 193–207

Bech J (1987) Les terres medicinales.. Discurso de Ingreso como membro numerário en la Real Académia de Farmacia de Barcelona

Bech J (1994) Contribuición al estudio de las arcillas de uso medicinal a lo largo de la história. Tesis doctoral en Farmacia, Facultad de Farmacia, Univ. Barcelona, 3 vol., I- 420pp, II-341pp; III – 299pp

Bech J (1996) Aspectos históricos y técnicos de las arcillas de uso medicinal. IX Simposio del Grupo Especializado de Cristalografia, Real Sociedad Española de Fisica y Quimica, Univ. Granada

Bech J (2010) Terra Lemnia: dades, dubtes i pelegrins, Discurso de Ingreso como académico numerário de la Real Académia de Medicina de Catalunya, 100pp

Bech J (2014) Algunas precisiones sobre la legendaria Terra Lemnia. Lição para obtenção do título de Doutor Honoris Causa pela Universidad Miguel Hernandéz, Elche, España

Beer S, Saely CH, Hoefle G, Rein P, Vonbank A, Breuss J, Gaensbacher B, Muendlein A, Drexel H (2010) Low bone mineral density is not associated with angiographically determined coronary atherosclerosis in men. Osteoporos Int 21:1695–1701

Belon P (1553) Voyage au Levant: Les observations de Pierre Belon du Mans de plusieurs singularities & choses mémorables trouvées en Grèce, Turquie, Judée, Egypte, Arabe & autres pays étrangers. Alexandra Merle (ed), Paris, Chandeigne, 2001, 109pp

Beniash E (2011) Biominerals-hierarchical nanocomposites: the example of bone. Rev Nanomed Nanobiotechnol 3(1):47–69. RP (1975)

Blakemore RP (1975) Magnetotactic bacteria. Science 190(4212):377–379

Bunnell JE, Finkelman RB, Centeno JA, Selinus O (2007) Medical geology: a globally emerging discipline. Geol Acta 5(3):273–281

Buseck PR, Jacob DJ, Pósfai M, Li J, Anderson JR (2000) Minerals in the air: an environmental perspective. Int Geol Rev 42:577–593

Carbajo JM, Maraver F (2017) Sulphurous mineral waters: new applications for health. Evid Based Complement Alternat Med 2017:8034084

Carbajo JM, Maraver F (2018) Salt water and skin interactions: new lines of evidence. Int J Biometeorol 62(8):1345–1360

Cardoso A (2017a) Hipócrates: "O Pai da Medicina". Medicina//Primórdios, Visão- História, n°40, 10–15

Cardoso A (2017b) Sífilis, o mal francês. Medicina//Primórdios, Visão- História, n°40, 34–37

Carretero MI, Pozo M (2007) Mineralogía aplicada: salud y medio ambiente. Thomson, Madrid, 464pp

Carretero MI, Pozo M (2009) Clay and non-clay minerals in the pharmaceutical industry, Part I: Excipients and medical applications. Appl Clay Sci 46:73–80

Carretero MI, Pozo M (2010) Clay and non-clay minerals in the pharmaceutical and cosmetic industries, Part II: Active ingredients. Appl Clay Sci 47:171–181

Centeno JA, Finlelman RB, Selinus O (2016) Medical geology: impacts of the natural environment on public health. Geosciences 6(1):8. https://doi.org/10.3390/geoscinces6010008

Chain Y, Illanes L (2015) Radiofármacos en medicina nuclear: Fundamentos y Aplicación Clínica. Facultad de Ciencias Exactas, Edulp (Editorial de la Universidad de la Plata, Libros de Cátedra, 188pp

Combes C, Cazalbon S, Rey C (2016) Apatite Biominerals Minerals 6(2):34. https://doi.org/10.3390/min6020034

Cottignoli V, Cavarretta E, Salvador L, Valfré C, Maras A (2015a) Morphological and chemical study of pathological deposits in human aortic and mitral valve stenosis: a biomineralogical contribution. Pathol Res Int 15, 342984, 14pp

Cottignoli V, Cavarretta E, Salvador L, Valfré C, Maras A (2015b) Biological niches within human calcified aortic valves: towards understanding of the pathological biomineralization process. Hindawi Publishing Corporation BioMed Research International Volume 2015

Cross W (1919) Geology of the world war and after. Geol Soc Am Bull 30:165–188

Davenhall B (2012) Geomedicine: geography and personal health. ESRI, Redlands. https://www.esri.com/library/ebooks/geomedicine.pdf

Davies BE, Bowman C, Davies TC, Selinus O (2005) Medical geology: perspectives and prospects. In: Selinus O, Alloway B, Centeno JA, Finkelman RB, Fuge R, Lindh U, Smedley P (eds) Essentials of medical geology: impacts of the natural environment on public health. Elsevier, Academic Press, pp 1–14

Demichelis R, Schuitemaker A, Garcia NA, Koziara K, De La Pierre M, Raiteri P, Gale JD (2018) Simulation of crystallization of biominerals. Annu Rev Mater Res 48:327–352

Dharmananda S (2012) Tibetan herbal medicine. https://www.itmonline.org/arts/tibherbs.htm

Diekema DJ, BootsMiller BJ, Vaughn TE, Woolson RF, Yankey JW (2004) Antimicrobial resistance trends and outbreak frequency in United States hospitals. Clin Inf Dis 38:78–85

Dong H, Lu A (2012) Mineral-microbe interactions and implications for remediation. Elements 8:95–100

Dove PM (2010) The rise of skeletal biominerals. Elements 6(1):37–42

Duffin CJ (2013) Lithotherapeutical research sources from antiquity to the mid-eighteenth century. In: History of geology and medicine. Geological Society Special Publication, London, pp 7, 375p–43

Duffin CJ, Moody RTJ, Gardner-Thorpe C (2013) A history of geology and medicine. In: Duffin CJ, RTJ M, Gardner-Thorpe C (eds) . Geological Society, London. Special Publication n° 375

Edmonds M, Grattan J, Michnowicz S (2018) Volcanic gases: silent killers. Adv Volcanol:65–83

Elliot JC (2002) Calcium phosphate biominerals. Rev Mineral Geochem 48(1):427–453

Endo K, Kogure T, Nagasawa H (2018) Biomineralization: from molecular and nano-structural analyses to environmental science. Springer, Singapore. ISBN:978-981-13-1001-0

Finkelman RB (2019) The influence of clays on human health: a medical geology perspective. Clays Clay Miner 58(2). Journal of Clay Minerals Society, ISSN:0009-8604. https://doi.org/10.1007/s42860-018-0001-9

Foster HD (2002) The geography of disease family trees: The case of selenium. In: Bobrowsky P, Balkema AA (eds) Geoenvironmental mapping: methods, theory and practice, pp 497–529

Garret RG (2000) Natural sources of metals in the environment. Hum Ecol Risk Assess 6(6):954–963

Gbadebo AM, Bankole OD (2007) Analysis of potentially toxic metals in airborne cement dust around Sagamu, Southwestern Nigeria. J Appl Sci 7:35–40. https://doi.org/10.3923/jas.2007.35.40

Gieré R, Vaughan DJ (2013) Minerals in the air. Mineral Matters Elem:410–411

Glick JB, Kaur RR, Siegel D (2013) Achieving hemostasis in dermatology – Part II: Topical hemostatic agents. Indian Dermatol Online J 4(3):172–176

Gomes CSF (2018) Healing and edible clays: a review of basic concepts, benefits and risks. Environ Geochem Health 40:1739–1765, Springer. https://doi.org/10.1007/s10653-016-9903-4

Gomes CSF, Silva JBP (2007) Minerals and clay minerals in medical geology. Appl Clay Sci 36:4–21

Gomes CSF, Carretero MI, Pozo M, Maraver F, Cantista P, Armijo F, Legido JL, Teixeira F, Rautureau M, Delgado R (2013) Peloids and pelotherapy: historical evolution, classification and glossary. Appl Clay Sci 75–76:28–38

Gomes CSF, Silva JBP, Viegas Fernandes J, Viegas Fernandes FM (2019) Thalassotherapy in Porto Santo Island of the Madeira Archipelago: Facts and Prospects. Bol Soc Esp Hidrol Méd 34(1):9–33. ISSN:0214-2813. https://doi.org/10.23853/bsehm.2019.0953

Gomes CSF, Gomes JH, Silva EF (2020) Bacteriostatic and bactericidal clays: an overview. Environ Geochem Health, Published online 30 June 2020, 21pp, Springer. https://doi.org/10.1007/s10653-020-00628-w

Hajsadeghi S, Khamseh M-E, Larijani B, Abedin B, Vakili-Zarch A, Meysamie A-P, Yazdanpanah F (2011) Bone mineral density and coronary atherosclerosis. J Saudi Heart Assoc 23:143–146

Hall AJ, Photos-Jones E (2008) Assessing past beliefs and practices: the case of Lemnian Earth. Archeometry 50:1032–1049

Hasan SE, Finkelman RB, Skinner HCW (2013) Geology and health: a brief history from the Pleistocene to today. The Geological Society of America Special Paper 501

IARC (1987) Silica and some silicates. Monographs 42

Lev E (2010) Healing with minerals and inorganic substances: a review of Levantine practice from the Middle Ages to the present. Int Geol Rev 52(7–8):700–725. https://doi.org/10.1080/00206811003679661

Limpitlaw UG (2004) The medical use of minerals, rocks and fossils. In: Proceedings of the Geological Society of America, Annual Meeting Abstract 48–5, 36(5):130

Limpitlaw U (2010) Ingestion of earth materials for health by humans and animals. Int Geol Rev 52(7–8):726–744. https://doi.org/10.1080/00206811003679695

López-Galindo A, Viseras C (2004) Pharmaceutical and cosmetic applications of clays. In: Wypych F, Satyanarayana KG (eds) Clay surfaces: fundamentals and applications. Elsevier Ltd, pp 267–289

López-Galindo A, Viseras C, Aguzzi C, Cerezo P (2011) Pharmaceutical and cosmetic uses of fibrous clays. Dev Clay Sci 3, Elsevier B.V. https://doi.org/10.1016/B978-0-444-53607-5.00013-X

Läg J (1990) General survey of geomedicine. In: Läg J (ed) Geomedicine. CRC Press, Boca Raton, pp 1–24

Maraver F (2017) Investigación actual en peloterapia. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, España, pp 33–35

Martin R, Dowling K, Pearce D, Sillitoe J, Florentine S (2014) Health effects associated with inhalation of airborne arsenic arising from mining operations. Geosciences 4:128–175. https://doi.org/10.3390/geosciences4030128

Martindale (1982) The extra pharmacopoeia. In: Reynolds JEF (ed) , 28th edn. The Pharmaceutical Press, London, pp 606–607: 938

Miller CF, Wark DA (2008) Supervolcanoes and their supereruptions. Elements 4:11–16

Morer C (2016) Talasoterapia. Bol Soc Esp Hidrologia Médica 31:119–146

Morrison KD, Misra R, Williams LB (2016) Unearthing the antibacterial mechanism of medicinal clay: a geochemical approach to combating antibiotic resistance. Sci Rep 6:19043. https://doi.org/10.1038/Srep19043

Novelli G (1996) Applicazion medicali e Igieniche delle bentoniti. In: Veniale F (ed) Atti Conv. “Argille Curative”. Gruppo Italiano AIPEA, Salice Terme (PV), Tipografia Trabella, Milano

Novelli G (1998) Applicazioni Cosmetiche e Medicaliu delle argille smectiche. Cosmet News 122:350–357

Novelli G (2000) Bentonite: A clay over the centuries. Incontri Scentifici, V Corso di Formazione “Metodi di Analisi di Materiali Argillosi”. Gruppo Itaiano AIPEA, pp 263–304

Nutton V (2004) Ancient medicine. Routledge, Oxon

Oliveira RP (2011) Para o Estudo da Saúde Conventual no Ínicio do Século XIX: As Boticas. Asclepio. Revista de História de la Medicina y de la Ciencia, v. LXIII, n°1, enero-junio, 123–154, ISSN:0210-4466

Oliveira R, Santos D, Ferreira D, Coelho P, Veiga F (2006) Preparações radiofarmacêuticas e suas aplicações. RBCF (Revista Brasileira de Ciências Farmacêuticas) 42(2):151–165

Orchardson R, Gillam DG (2000) The efficacy of potassium salts as agents for treating dentin hypersensitivity. J Orofac Pain 14(1):9–19

Otto CC, Haydel SE (2013) Exchangeable ions are responsible for the in vitro antibacterial properties of natural clay mixtures. PLos One 8(5):1–9

Photos-Jones E, Hall AJ (2011) Lemnian earth and the earths of the Agean: an archeological guide to medicines, pigments and washing powders. Potinguir Press, Glasgow

Photos-Jones E, Christidis GE, Piochi M, Keanee C, Mormone A, Balassone G, Perdikatsis V, Leanord A (2016) Testing Greco-Roman medicinal minerals: The case of solfataric alum. J Archaeol Sci Rep 10:82–95

Photos-Jones E, Edwards C, Haner F, Lawton L, Keane C, Leanord A, Perdikatsis V (2017) Archaeological medicinal earths as antibacterial agents: the case of the Basel Lemnian sphragides. In: Duffin CJ, Gardner-Thorpe C, Moody RTJ (eds) Geology and medicine: historical connections. Geological Society, London, Special Publications 452. https://doi.org/10.1144/SP452.6

Pierre-Louis B, Aronow WS, Yoon JH, Ahn C, Deluca AJ (2009) Relation of bone mineral density to stress test-induced myocardial ischemia. Am J Cardiol 104(2):199–201

Pita JR (1999) Um Livro com 200 anos: A Farmacopeia Portuguesa (edição oficial): A publicação da primeira farmacopeia oficial: Pharmacopeia Geral (1794). Revista de História de Ideias 20:47–100

Pita JR, Pereira AL (2012) A arte farmacêutica no século XVIII, a farmácia conventual e o inventário da Botica do Convento de Nossa senhora do Carmo (Aveiro)/Pharmaceutical Art in the 18th century, Conventual Pharmacy and the Inventory of the Apothecary of the Convento of Nossa Senhora do Carmo (Aveiro). Ágora, Estudos Clássicos em Debate 14(1):227–268. ISSN:0874-5498

Posfai M, Molnar A (2000) Aerosol particles in the troposphere: a mineralogical introduction, in EMU Notes in Mineralogy 2, Enviromental Mineralogy, chapter 10, eds. Vaughan DJ, Wogelius RA, Eotvos University Press, Budapest

Prospero JM (2001) African dust in America. Geotimes 46(1):24–27

Rautureau M, Liewig N, Gomes CSF, Katouzian-Safadi M (2010) Argiles et Santé: Propriétés et Thérapies. Editions Médicales Internationales, Lavoisier, 184 pp, ISBN:978-2-7430-1202-1

Rautureau M, Gomes CSF, Liewig N, Safadi MK (2017) Clays and health: properties and therapeutic uses. Springer, Cham. ISBN:978-3-319-42883-3

Retsas S (2012) Medicinal use of earths and minerals from Hippocrates to Sir Hans Sloan and beyond. Vesalis, XVIII, 93–98

Retsas S (2016) Geotherapeutics: the medicinal use of earths, minerals and metals from Antiquity to the twenty-first century. Geological Society, London, Special Paper, v.452. https://doi.org/10.1144/SP452.5

Rosborg I (ed) (2015) Drinking water, minerals and mineral balance: importance, health significance, safety precautions. Springer, Cham, 140pp

Ruiz-Hitzky E, Darder M, Alcântara A, Wicklein B, Aranda P (2015) Recent advances on fibrous clay-based Nanocomposites. Adv Polym Sci 267:39–86

Sánchez IP (2001) Radiofármacos PET. Ver Esp Med Nuclear 20:477–498

Satish S, Tharmavaram M, Rawtani D (2019) Halloysite nanotubes as a nature's boon for biomedical applications. Nanomedicine 6:1–16

Selinus O, Alloway B, Centeno J, Finkelman R, Fuge R, Lindh U, Smedley P (eds) (2005) Essentials of medical geology: impacts of the natural environment on public health. Elsevier Academic Press, 812p

Selinus O, Finkelman R, Centeno J (2010) Medical geology: a regional synthesis. Springer, 392pp. ISBN:978-90-481-3429-8. https://doi.org/10.1007/978-90-481-3430-4

Skinner HCW (2000) Minerals and human health. In: Vaughan J, Wogelius RA (eds) EMU notes in mineralogy 2, environmental mineralogy. Eotvos University Press, Budapest, pp 383–412

Skinner HCW (2005a) Biominerals. Mineral Mag 69(5):621–641

Skinner HCW (2005b) Mineralogy of bone. In: Essentials of medical geology: impacts of the natural environment on public health. Elsevier/Academic Press, New York, pp 607–693

Spalek K, Spielvogel I (2019) The use of medicinal clay from Silesia "Terra Sigillata Silesiaca", Central Europe – a new change for natural medicine? Biomed J Sci Tech Res 20(3):BJSTR. MS. ID.003457. https://doi.org/10.26717/BJSTR.2019.20.003457

Sun J, Li Y, Liang X-J, Wang PC (2011) Bacterial magnetosome: a novel biogenetic magnetic targeted drug carrier with potential multifunctions. J Nanomater 2011:469031, 13 p. https://doi.org/10.1155/2011/469031

Teixeira F (2009) Água, fonte da vida. In: Comissão de Coordenação e Desenvolvimento da Região Centro (ed) À Beira da Água, pp 109–139. ISBN:978-972-569-160-1

Teixeira F (2010) La utilización de las lamas en Portugal: Passado y Presente. II Congreso Iberoamericano de Peloides, Balneário de Lanjarón. Libro de Resúmenes (Maraver F y Carretero M I, editores), 14–15

Teixeira F (2012) O Termalismo na Região Centro. Capítulo XIII do livro "Águas Minerais Naturais e de Nascente da Região Norte", Simões Cortez JA (Coordenador), Mare Liberum, FEDRAVE (editor), 261–300

Teixeira F (2016) Termalismo terapêutico em Portugal: Presente e perspectivas futuras. Revista Factores de Risco, Sociedade Portuguesa de Cardiologia 41:26–37

Teixeira F (2017) O Termalismo na Região Norte. Capítulo IV do livro "Águas Minerais Naturais e de Nascente da Região Norte", Simões Cortez JA (Coordenador), Mare Liberum, FEDRAVE (editor), 159–193

Thompson CJS (1914) Terra Sigillata, a famous medicamente of ancient times. In: Proceedings of the 17th international Congress of Medicine 23:433–434

van Thienen G, Spee T (2008) Health effects of construction materials and construction products. Tijdschrift voor toegepaste Arbowetenschap, TTA brochure nr 1

Varma R, Aronow WS, Basis Y, Singh T, Kalapatapu K, Weiss MB, Pucillo AL, Monsen CE (2008) Relation of bone mineral density to frequency of coronary heart disease. Am J Cardiol 101:1103–1104

Venieri D, Gounaki I, Christidis GE, Knapp CW, Bouras-Vallianatos P, Photos-Jones E (2020) Minerals. MDPI 10:348. https://doi.org/10.3390/min10040348

Vermed F, Vicente J, Hidalgo-Álvarez R (2009) Physical properties of elongated magnetic particles: magnetization and friction coefficient anisotropies. ChemPhysChem 10(8):1165–1179

Viseras C, López-Galindo A (1999) Pharmaceutical applications of some Spanish clays (sepiolite, palygorskite, bentonite): some pre-formulation studies. Appl Clay Sci 14:69–82

Viseras C, López-Galindo A (2000) Characteristics of pharmaceutical grade phyllosilicate powders. Pharm Dev Technol 5(1):47–52

Viseras C, Aguzzi C, Cerezo P, Lopez-Galindo A (2007) Uses of clay minerals in semisolid health care and therapeutic products. Appl Clay Sci 36:37–50

Viseras C, Carazo E, Borrego-Sanchez A, Garcia-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C (2019) Clay minerals in skin drug delivery. Clay Clay Miner. https://doi.org/10.1007/s42860-018-0003-7

Wara-Aswapati N, Krongnawakul D, Jirarviboon D, Adulyanon S, Karimbux N, Pitiphat W (2005) The effect of a new toothpaste containing potassium nitrate and triclosan on gingival health, plaque formation and dentine hypersensitivity. J Clin Periodontol 32(1):53–58. https://doi.org/10.1111/j.1600-051X.2004.00631.x

Williams RS (1986) The fascinating history of bezoars. Med J Aust 145:613–614

Williams LB and Haydel SE (2010) Evaluation of the medicinal use of clay minerals as antibacterial agentes. Int Geol Ver 52(7/8):745–770. https://doi.org/10.1080/00206811003679737

Williams-Jones G, Rymer H (2015) Hazards of volcanic gases, 2nd edn. The Encyclopedia of Volcanoes, pp 985–992

Yan L, Zhang S, Chen P, Liu H, Yin H, Li H (2012) Magnetotactic bacteria, magnetosomes and their application. Microbiol Res 167:507–519. Elsevier

Yeshi K, Wangdi T, Namgyal Q, Nettles J, Craig SR, Schrempf M, Wangchuk P (2018) Geopharmaceuticals of Himalayan Sowa Rigpa medicine: Ethnopharmacological uses, mineral diversity, chemical identification and current utilization in Bhutan. J Ethnopharmacol 223:99–112

Yu W, Foster HD, Zhang T (1995) Discovering Chinese mineral drugs. J Orthomol Med 10

Zhou CH, Keeling J (2013) Fundamental and applied research on clay minerals: from climate and environment to nanotechnology. Appl Clay Sci 74:3–9

Chapter 4
Health Benefits and Risks of Minerals: Bioavailability, Bio-Essentiality, Toxicity, and Pathologies

Celso S. F. Gomes and Eduardo A. F. Silva

Abstract The chapter starts with the uptake of minerals in the elemental form by the human body, minerals that could be either beneficial or harmful, the uptake involving four sources (food, soil, water, and air) and three pathways (ingestion, inhalation, and dermal absorption). Afterward the minerals' geochemical classification, exposure, bioavailability, bioaccumulation, bio-essentiality, and toxicity are the subjects dealt with. Man and minerals are chemical systems which have in common in their constitution of chemical elements or minerals called major, minor, and trace which are essential not only for life and life quality but for minerals formation too. Even these bio-essential minerals in the elemental form can provide toxicity caused by excess and deficiency. Sources and pathologies that can be caused by potentially toxic minerals in the elemental form and by some minerals stricto sensu are identified and discussed. Some metals are essential for life, living quality, and health conditioning, as essential constituents of metalloproteins and metalloenzymes. Some metals, as is the case of heavy metals, may cause health hazards. Nutritional supplements based on minerals and vitamins are dealt with. The chapter ends with the health risks caused by airborne minerals existing in both natural and anthropogenic dust, gas, ash, and smoke.

C. S. F. Gomes (✉) · E. A. F. Silva
Department of Geosciences, Researcher of the Research Unit "GeoBioTec",
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt; eafs@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_4

4.1 Sources and Pathways of the Uptake of *Minerals l.s.* by the Human Body

The uptake by the human body of minerals *l.s.*, either beneficial or harmful to humans, takes place from four sources: *food* (through ingestion of plant and animal products), *soil* (through the practice called *geophagy*), *water* (through ingestion), and *air* (through the inhalation of airborne dust).

The ultimate source of minerals *l.s.* is the natural environment. In the case of minerals in the elemental form, the so-called essential nutrients are obtained by eating plants that accumulated these elements from the soil; by eating meat from animals that accumulated the elements from plants or from animals that had obtained the elements from plant-eating organisms lower in the food chain; by drinking water in which the nutrients are suspended or dissolved; or by directly ingesting clayey soil or edible clay (geophagy).

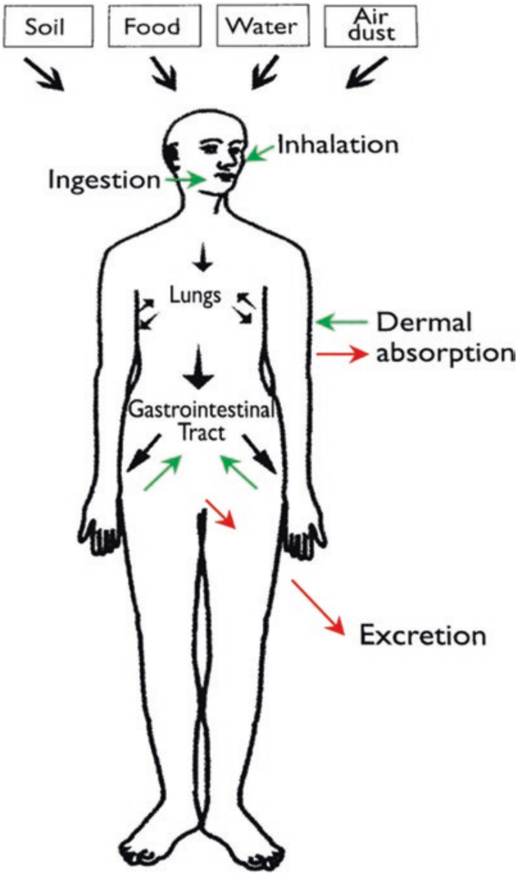


Fig. 4.1 Sources and pathways of *minerals/chemical elements uptake by the human body*. (Source: Adapted from Fergusson 1990)

Today many people rely on vitamin/mineral pills to augment their daily requirements of the essential elements, but the minerals, effectively chemical elements, in those pills are ultimately derived from rocks, minerals *s.s.*, or natural waters.

There are three pathways for minerals to enter the human body: *ingestion*, *inhalation*, and *dermal absorption* (Fig. 4.1).

Ingestion is the most frequent route of exposure for most people, whereas *inhalation* and *dermal absorption* are relevant only to people with certain occupations or living in certain regions and places where there is airborne dust (Adriano 2001).

Human beings need a regular supply of food and water (1–2 liters per day) and an essentially continuous supply of air (10–20 m^3 per day). The WHO recognizes as a fundamental human right that all people should have free access to air and water, both of acceptable quality.

The essentiality of certain chemical elements for human health, only with the advent of *Modern Medicine* in the nineteenth century, has been scientifically recognized (Bowman et al. 2003).

Once inside the body, the incorporation of a certain chemical element depends on several factors, for example, the nutritional status of the individual and the size of the particle that contains the element.

According to Bowman et al. (2003), harmful elements may be present in the environment or in high and toxic levels of concentration, putting health at risk, or in poor concentration levels without putting health at risk.

4.2 Mobility, Exposure, and Bioavailability of Minerals

The concept of the term *minerals* in this subheading essentially corresponds to the chemical elements that are present in the natural environment in individual and free forms which can be incorporated into the human body providing health benefits/risks.

In the natural environment and from a geochemical point of view, the *natural chemical elements* are classified into five empirical groups or categories (Goldschmidt 1954):

1. *Atmophilics* (H, O, and N): dominant in the atmosphere.
2. *Siderophilics* (Fe, Ni, Co, Pt, Au, Mo, Ge, Sn, C, and P): some like Fe and Ni are dominant in the terrestrial nucleus; others are rare in the terrestrial crust.
3. *Calcophilics* (Cu, Ag, Zn, Cd, Hg, Pb, As, S, and Te): having affinity for S participate in the formation of sulfides and sulfates.
4. *Lithophilics* (Na, K, Li, Rb, Cs, Mg, Ca, Sr, Ba, and Al, and REE, rare-earth elements): dominant in the terrestrial crust and having affinity for Si and O, participate in the formation of silicates.
5. *Biophilics* (C, H, O, N, P, S, Cl, and I) – major elements and (B, Ca, Mg, K, Na, V, Mn, Fe, and Cu) – minor elements: particularly the major elements are enriched in the *biosphere* and participate in the organisms composition.

The current meaning of *biosphere* within an ecological context can be traced back to Vernadsky (1926) who provided an important contribution to the understanding of the interaction of the living and nonliving earth systems. Vernadsky's view of the *biosphere* was a new way of looking at our planet (Hannigan 2007).

The *lithophilic* elements being dominant in the terrestrial crust, when in ionic form, compete with each other and with the ions of other elements in order to form a great number of mineral species and mineral varieties, explained by the four rules of Goldschmidt, scientist later known as the "father of Modern Geochemistry":

1. In the formation of the crystalline structures of minerals, the ions of one element can replace the ions of another element if the respective ionic rays do not differ by more than 15%.
2. Ions whose electrical charges do not differ by more than one unit of charge may be substituted if the electrical neutrality of the crystalline structure of the mineral is maintained.
3. If two ions are competing to enter a given crystal structure, the ion with the greatest ionic potential (expressed as the electric charge/ion beam ratio) is the preferred one.
4. Ionic substitution is limited when competing ions differ in electronegativity and form chemical bonds of different ionic character.

The classification and rules just mentioned are fundamental to explain the occurrences in the natural environment of potentially toxic elements and to predict where such occurrences can be found, very important situations in *Medical Geology*. Mineral elements or natural chemical elements, depending on their essentiality or toxicity to human health, are classified as *essential* and *toxic elements*.

Atomic or ionic substitutions as well as atomic or ionic omissions are point-specific structural defects common in minerals, naturally more often than in others, which greatly influence their stability and activity, for example, facilitating interaction with the fluids of the upper crust and with the surface waters and, consequently, the solvability and the passage of the constituent ions of the crystalline structures to the free state.

Hollabaugh (2007) proposed modifications to the Goldschmidt's geochemical distribution and classification of the chemical elements in order to include arsenic (As), mercury (Hg), and lead (Pb), traditional *chalcophile* elements, as *biophile* elements, since they have great affinity to concentrate in the biosphere. Really under certain conditions, they can reach relatively high concentrations in humans with toxic hazardous consequences in what health is concerned. They are *biophile* because of atomic substitutions (e.g., lead for calcium), bioaccumulation (arsenic and mercury), and methylation (mercury).

C, H, O, N, P, S, Cl, and I (major elements) and B, Ca, Mg, K, Na, V, Mn, Fe, and Cu (minor elements) are the well-established *biophile* elements.

The surfaces of minerals when exposed are also reactive with atmospheric gases and liquid aerosols.

Hochella (2002) presents examples of the role of minerals in environmental science. The exposure and, more importantly, the *bioavailability*, i.e., the fraction of the chemical or mineral element that is effectively incorporated, depend on the following factors:

1. Concentration at the source;
2. Particle size;
3. Specific physical and chemical properties of the contaminant itself.

For example, thorium (Th) forming part of the structure of the mineral zircon ($ZrSiO_4$) isomorphously replacing zirconium (Zr) is not hazardous because it is not bioavailable in free form, zircon being a mineral of extraordinary stability in the natural environment.

Dissnayake and Chandrajith (2006) emphasize that the mere presence of a potential toxic element or of a potential toxic element species does not necessarily imply a health hazard; essentiality or toxicity depends on two main factors: *bioavailability* and *bioaccumulation*. It is by meteoric or deuteric alteration of the rock-forming minerals that the chemical elements present in these minerals can pass to the free state, and, in this state, some may be more mobile and bioavailable than others, the *degree of mobility* depending on the environmental physicochemical conditions, essentially pH (acid, alkaline, or neutral) and Eh potential (oxidant or reducing).

The potential for a chemical element to cause health problems depends not only on its short or long presence and concentration but also on its speciation because it controls mobility and, of course, distribution in the environment. The speciation of the element (metal or metalloid), i.e., the electrical valence of the element, influences bioavailability and bio-accessibility and possible toxicity. For example, arsenic (As) can be present in four valence states (0, 3, 5, and 3^- (gas)), and, in the environment, it can be part of inorganic and organic compounds. The trivalent species [As(III)] is more stable in a reducing environment, while the pentavalent species [As(V)] is more stable in an oxidizing environment. It is also demonstrated that biologically the inorganic form of As is about 100 times more toxic than the organic forms and that As(III) is about 60 times more toxic than the As(V) form (Ferguson and Gavis 1972).

According to Bogden et al. (1997), bioavailability may be influenced by dietary factors. It is the case that gastrointestinal Pb uptake can be substantially reduced with a relatively high Ca diet.

Table 4.1 shows that the mobility of some chemicals considered important for human health, because they may be beneficial or harmful, depends on certain physicochemical conditions of the environment in which they are found. However, other factors may influence the mobility, such as soil type, climate, precipitation, geomorphology, vegetation cover, and microbiological activity. But the mobility of the usual geogenic contaminants (e.g., As, F, Cd, Hg, Pb, Se, U, and Rn) can also result from anthropogenic processes.

Geogenic contaminants can affect human health, or through primary consumption (e.g., water intake or solid geological materials in the case of geophagy), or bioaccumulation through the food chain.

Table 4.1 Mobility of certain chemical trace elements in distinct surface environments with positive or negative impacts on human health

Mobility degree	Environmental conditions	Trace elements
High	Acid, neutral, or alkaline	V, Zn
	Acid and oxidizing	Se, Cd, Hg, Cu, Ag, Zn
Medium	Mainly acid	Ag, Se, Cd, Co, Cu, Ni, Hg
	Reducing of variable potential	As, Cd, Co, Cr, Mn, V
Low	Neutral or alkaline	Co, Cu, Mn, Ni
	Acid and oxidizing	Cr, Se
Very low	Neutral or alkaline	Ag, Cu, Co, Ni
	Reducing	Ag, As, Cd, Co, Cu, Hg, Mo, Ni, Pb, V, Zn

Source: Kabata-Pendias

Inhalation (e.g., dusts and aerosols) and *dermal absorption* (e.g., when topical application of *curative* or *healing muds*, peloids included) are the other routes of the incorporation of contaminants.

According to Williams (2005), regarding the incorporation of chemical elements, biological ecosystems are dependent on the geosphere. In fact, the environment cannot be considered apart from the chemical systems of life and its evolution. Initially, the mineral elements are absorbed or incorporated by the plants, and these are transferred to the animals through cooperative organization processes.

Empirical knowledge related to human health, whose treatment and practice is called "empirical medicine" or "Galenic medicine," is essential in many aspects of human life and activity. However, in this regard, man's quest for rational explanations based on science and technology is equally essential. Effectively, with perseverance, step by step, using accumulated experience and scientific information, fundamental and applied, due to specialists from different fields and scientific fields (chemistry, biochemistry, biology, biotechnology, mineralogy, geochemistry, hydrochemistry, materials science, medicine, public health, pharmacy, nutrition, and others), man was able to increase the degree of knowledge regarding the interaction between minerals and other geological resources with human health.

Man and *minerals* are chemical systems made up of chemical elements or minerals called *major* and *minor* in common, such as oxygen, hydrogen, carbon, sulfur, calcium, magnesium, sodium, potassium, and phosphorus, and some other chemical elements called *trace elements* or *trace minerals* such as iron, selenium, copper, zinc, iodine, manganese and fluorine, which are essential not only for life and life quality but for minerals formation too.

In the natural environment where man lives, *minerals s.s.* and *chemical elements* are omnipresent, varying their quality and quantity with the nature of geological materials, more precisely of the type of rock (granite, basalt, limestone, shale, clay, etc.); the concentration of some elements depends, for example, on the igneous rock being acidic or basic, and also, for example, that heavy metals tend to concentrate on rocks rich in clay minerals and organic materials.

The elimination of toxic and nontoxic chemical elements takes place through the excretion of organic fluids (sweat and urine) and metabolites (feces). Within the body the minerals participate in the metabolic reactions and are distributed in the tissues through the bloodstream, after which they are absorbed. In order for the body to benefit from good health, it is necessary to maintain an adequate balance with regard to the minerals present in the human body.

Minerals can interact with each other and with other nutrients. The so-called major chemical elements or mineral salts, or the so-called trace elements or trace minerals, when taken in excess through diets or supplements, can produce *toxicity*.

Toxicology is the science whose objective is: "The assessment and management of risks due to called xenobiotics (elements or chemical compounds that are foreign to or introduced into the human body, either in quantities greater than admissible, or through other pathways other than those occurring in normal metabolism)."

The kidneys when they work well can regulate the concentrations of minerals in the body by excreting excesses in the urine.

Inhalation is also another route of entry of minerals into the human body carried in the form of dust, fumes, and aerosols. There are people who have professional occupations involving the exploitation of mineral resources, in mines and quarries that inhale mineral dust, which can result in diseases of the respiratory system, such as silicosis and *asbestosis*, which can be lethal. The *inhalation* of mineral particles present in aerosols and their deposition in the lung alveoli of man can cause health problems depending on the composition, size, and shape of the particles. Particles of silicates smaller than 5 μm (1 μm = 10^{-3} mm) having fibrous habits usually penetrate deeper into the lungs than larger particles, and the particles could become fixated and cause *silicosis* and *asbestosis*. The *inhalation* of fine particles of other minerals, silicates or nonsilicates, by persons involved in certain occupational activities, can cause respiratory system disorders or pathologies, such as *talcosis*, *stenosis*, *berylliosis*, and *baritosis*.

Dermal absorption is yet another entryway of minerals into the human body; it occurs along the process of topical application of dermocosmetics, dermotherapeutics, healing muds, and peloids, and also along the application of *medicinal mineral water* by *thermal baths*, by *seawater baths in thalassotherapy*, and also by *sand baths* in *psammotherapy*.

4.3 Metals, Life, Living Quality, and Health Conditioning

Hazen (2009), a researcher at the Carnegie Geophysical Laboratory in Washington, USA, believes that minerals and life on Earth have progressively evolved and become increasingly complex, in organization and diversification. When the solar system formed, there was no more than a dozen different *minerals s.s.* that became organized within the existing chemical elements. With the formation of the Earth about 4.5 Ga years ago, followed by the formation of a hydrosphere and continental crust as early as 4.3 Ga years ago, and through the action of geochemical processes whose evolution has increased in complexity, the number of mineral species has increased to about 500.

By definition mineral species is attributed to the group of individual minerals that have in common the same crystalline organization or crystalline structure and the same chemical composition, which may present small changes due to the so-called atomic isomorphism so common in minerals. But since the beginning of life, it has been assumed to have taken place some 3.8 billion years ago; most likely in the ocean formed some 4.0 billion years ago, with the transition from geochemistry to biogeochemistry processes and with the evolution of them, the number of mineral species has grown steadily, at present, to a number close to 4500, that is to say, about the number of species of mammals existing on Earth, due to the effect of the so-called biogeochemical processes. And an average of 50 mineral species is discovered and described each in passing year (Hazen 2009).

The meteoric and hydrothermal alterations of minerals of the rocks take place when they are exposed to weathering in the continental crust surface, the hydrothermal alteration being promoted, for instance, in the hydrothermal chimneys that occur in certain places of the oceanic crust. Both alteration processes referred to lead to the release of the elements present in the minerals, including the so-called metals. Metals occur naturally in small quantities in the soil, water, and air, in the elemental form. From the air, the humans can inhale metals in particulate and vapor forms, and from soil and water, humans consume metals through food and water.

In the periodic table, over 75% of the elements are metals and 8 (eight) are metalloids. People are exposed to metals through the food we eat, the water we drink, and the polluted air we breathe, as well as the medicines we take. Metals can form alloys with each other and with nonmetals (Morris 1992).

Man has used metals since the antiquity, as are the cases of gold (Au), silver (Ag), copper (Cu), lead (Pb), iron (Fe), tin (Sn), and mercury (Hg). Metals are substances found naturally in the Earth's crust, which are characterized by high electrical conductivity, malleability, and luster; metals voluntarily lose their electrons to form cations.

Some metals are called *heavy metals* if their specific density is higher than 5 g/cm^3, and it is well established that heavy metals adversely can affect the environment and living organisms (Järup 2003). Even the *heavy metals* when in low concentrations can maintain various biochemical and physiological functions in the living organisms. However, the same metals can become noxious when their concentrations exceed certain concentrations. Many different sources, classified as natural or anthropogenic, contribute metals to the environment with eventual implications on human health. The mineralogical or chemical form in which a metal occurs in the source will greatly affect how readily it is released into the environment. Examples of natural metal sources are rocks and soils, volcanic emissions, undersea smokers, and extraterrestrial material.

Examples of anthropogenic metal sources are as follows: mining, mineral processing and metal smelting, mine waste piles and tailings, mine-drainage waters, fertilizers, pesticides, sewage sludge, auto emissions, and coal combustion for power generation, municipal waste incineration, and landfills.

It is known that the more primitive life recorded and preserved in rocks is similar to that of modern bacteria. In the pathway of the simple inorganic molecules containing C, H, O, N, P, and S to the cells of the bacteria, there must have been precursor entities similar to the cells of the bacteria. This corresponds to the transition from geochemistry to biogeochemistry, a process that is central to determining the origin of life.

The concept of life is not unanimous among scientists, but it is widely accepted that all life forms have three fundamental characteristics (Sahai et al. 2016):

1. All cells have a double-walled membrane consisting of lipids that defines the boundaries of the cell and through which mass and energy flows occur and allows the transmission of signals between the cell and the surrounding environment.
2. All cells include a universal DNA-RNA-based device that acts to transmit genetic information from one generation to the next generation, a device capable of presenting important mutations in order to allow evolution by natural selection.
3. All cells need to possess metabolism, which can be described by the cycles of enzymes catalyzed by electron transfer reactions that allow the synthesis (anabolization) and decomposition (catabolization) of complex molecules.

All these processes provide the necessary molecules and energy with which the cell can be sustainable and reproduce.

Related to the three fundamental life features mentioned above are the corresponding molecular building blocks of life, namely, cell membrane-forming phospholipids, DNA/RNA and proteins, and a variety of critical small molecules such as adenosine phosphates. While it is difficult to define life, it is widely accepted that cell-like entities called pro-cells had all the characteristics of cells and preceded the so-called universal common ancestor, the organism from which all living beings now known descend.

Currently, most of the prokaryotes (bacteria and archea) constitute communities living in modern biofilms clinging to mineral surfaces (as is the case of the biofilm that lines the walls of the tank where the mud used in the Balneário da Coroa, Ribeira Grande, São Miguel, the Azores archipelago), so it is reasonable to assume that the mineral-water interface would have provided a maternity for protocells and that minerals, such as clays and metal sulfides of Fe, Mn, and Ni, played an important role in the synthesis and primitive protocells.

According to Southam (2012), conceptually minerals represent the important "substrates," that is, the sources of nutrients and energy for prokaryotes (because they can only transfer soluble compounds into or out of their cells. Effectively prokaryotes are able to utilize a wide variety of minerals such as energy sources, nutrients (metals), and electron receptors. They can directly oxidize or reduce the compounds of metals such as As, Cu, Cr, Fe, Mn, and Mo, affecting the bioavailability of these metals.

The great diversity that the mineral world presents is justified by the great diversity of environments in which minerals can be formed in terms of physical properties (temperature and pressure), chemical properties (such as chemical composition, oxidation, reduction, acidity, basicity, and humidity), and biochemical properties. Variations in the properties of the environment may also lead to variations in the stability of the minerals, which may lead to the formation of new minerals. It is presently believed that the diversification of minerals is not only due to the diversity of geological processes but, essentially, to the appearance and evolution of life; it is very dependent on the appearance of oxygen and water on planet Earth.

It would have been the cyanobacteria that became abundant in the oceans, the first organisms capable of performing photosynthesis, an oxygen-producing process. This oxygen whose accumulation progressively raised would have promoted the substantial modification of the Earth's atmosphere and leading to the formation of new minerals in the earthy materials from the oxidation associated with the hydration of minerals, essentially the sulfides of various metals, such as iron, manganese, copper, nickel, cobalt, and lead, resulting in the production, for example, of carbonates, oxides, and sulfates, hydrated or not hydrated: *malachite*, *turquoise*, *azurite*, *hematite*, *magnetite*, *anhydrite*, *gypsum*, and *anglesite*.

According to Hazen (2009), only the oxidation would have promoted the formation of about 3000 new mineral species. The so-called Great Oxidation Event (GOE) did take place at around 2.5 Ga, and an oxygen-rich atmosphere was formed, the oxygen being derived from the photosynthesis process promoted by cyanobacteria whose activity in shallow sea environments originated carbonate-rich platforms and banded iron formations (Altermann et al. 2006; Konhauser et al. 2011).

Once life emerged on Earth, the living organisms, starting with the microorganisms like microbes as the primordial life-forms, soon have interacted with minerals. Minerals have provided nutrients and energy to the microorganisms whose activity provided biochemical alterations on minerals, changing the oxidation state of certain constituent elements as well as mineral solubility and the release of such elements, metals included (Dong 2012; Dong and Lu 2012). The biochemical processes associated with the GOE may thus be responsible, directly or indirectly, for most of Earth's 4400 known mineral species (Sverjensky and Lee 2010).

The oxygen (O) and hydrogen (H), and the combination of these elements in the form of water, are the main mineral-forming elements, entering in the chemical composition of silicates, carbonates, phosphates, sulfates, etc.

In a very recent article, Schoonen and Smirnov (2016) admit that in a short time after the formation of the Moon, which would have occurred about 4500 million years ago after a collision of the Earth with a meteorite of enormous size, then the higher concentration of CO_2 that promoted the so-called greenhouse effect would have accelerated the chemical alteration of the primitive crust and created favorable conditions for the conversion of inorganic carbon and nitrogen to the formation of the so-called primitive blocks of life promoted by clay, zeolites, sulfides, and metals, all potential catalysts, formed as the crust reacted with the carbonated warm water of the ocean.

Since the 1950s, there has been increasing interest and increasing research in the attempt to identify the origin or origins of life. There are two principal hypotheses about the origin of the simple prebiotic organic molecules: *terrestrial* or *endogenous* and *extraterrestrial* or *exogenous*. In both hypotheses, minerals had played important roles. About this subject, see Chap. 8 of this book entitled *Minerals and* *the Origin of Life*. When, where, and how did life on Earth originate and evolve are still unsolved scientific questions.

The chemical links between the environment and human health are often not easy to identify and understand because the biogeochemical mechanisms affecting human health are not known. The importance of the aforementioned bonds of the universal physical-chemical principles in the human body and in the natural geological environment was already expressed in the classic textbooks on bio-organic chemistry (Williams and Fraústo da Silva 1996), involving the interaction of inorganic chemical elements, metals, and others, with biomolecules. Such books which are considered as being the "bibles" of bioinorganic chemistry, show the cooperative functional activities between inorganic chemical elements and biological systems. Since then the scientific progresses in the area of biogeochemistry have been remarkable.

The lack of knowledge about the biogeochemical mechanisms of molecules funtioning may be outdated as recent studies leading to the award of the *Nobel Prize for Chemistry 2017* to researchers Jacques Dubochet, Joachim Frank, and Richard Henderson. These scientists were responsible for the development of a technique called *electron cryomicroscopy*, the samples of biomolecules in solution into organic fluids are frozen by ultrafast cooling at −196 degrees Celsius, a condition that prevents the formation of "ice" crystals, obtaining three-dimensional images of our cells revealing their structures with incomparable detail until the resolution at the atomic level, raising biochemistry and biogeochemistry to a new and high level of knowledge, a new look at the molecules of life. It will be possible to know much more about diseases and develop new drugs.

Life, as we know it today, is completely dependent on metals in the ionic state, and the concentration gradients of these metals are the engines of metabolism. Metals are constituents of minerals, the natural components of the Earth's crust. Metals can be beneficial or adverse for human health. In Chap. 5 of this book, relevant information on the interaction metals/human health is disclosed.

Goyer et al. (2004), concerning the human health effects of metals, have proposed four groups of metals:

1. Nutritionally essential metals (Co, Cr(III), Cu, Fe, Mn, Mo, Se, and Zn)
2. Metals that may have some beneficial effect (B, Ni, Si, and V)
3. Metals with no known essential or beneficial effects (Al, Sb, As, Ba, Be, Cd, Pb, Hg, Ag, Sr, and Tl)
4. Poisonous and carcinogenic metals (As, Cd, Cr(VI), Be, and Ni)

Metals are substances found naturally in the Earth's crust, which are characterized by high electrical conductivity, malleability, and luster, metals which voluntarily lose their electrons to form cations.

As aforesaid some metals are called heavy metals if their specific density is higher than 5 g/cm^3, and it is well established that heavy metals adversely can affect the environment and living organisms (Järup 2003). Even the heavy metals when in low concentrations can maintain various biochemical and physiological functions in the living organisms. However, the same metals can become noxious when they exceed certain concentrations.

Many different sources, classified as natural or anthropogenic, contribute metals to the environment with eventual implications on human health. The mineralogical or chemical form in which a metal occurs in the source will greatly affect how readily it is released into the environment.

Examples of natural metal sources are rocks and soils, volcanic emissions, undersea smokers, and extraterrestrial material. Examples of anthropogenic metal sources are mining, mineral processing and metal smelting, mine waste piles and tailings, mine-drainage waters, fertilizers, pesticides, sewage sludge, auto emissions, and coal combustion for power generation, municipal waste incineration, and landfills.

Of the 92 naturally occurring elements, approximately 30 metals and metalloids are potentially toxic to humans (Ag, Al, As, Au, B, Ba, Be, Bi, Cd, Co, Cr, Cs, Cu, Hg, Li, Mn, Mo, Ni, Pb, Pd, Pt, Sb, Se, Sn, Sr, Te, Ti, V, and W) (Morais et al. 2012) and the hazardous ones in terms of toxicity are the so-called *heavy metals*, a generic term used for metallic elements having atomic weights higher than 40.04, the value of Ca atomic mass (Ming-Ho 2005).

Very recently Singh and Sharma (2018) had produced an excellent paper on “Metal-Based Therapy in Traditional and Modern Medicine Systems,” included in a book entitled *Biomedical Applications of Metals* (Rai M et al. (editors) published by Springer International Publishing AG), that is a real milestone on the role of metals in biomedicine. According to Singh and Sharma (2018), in the modern medicine systems, metals are used as therapeutic agents in various ways. Radioactive metals are mostly used for diagnostic purposes, either as diagnostic medical imaging or as contrast agents, for example, in magnetic resonance imaging (MRI); and other metals are used for the cure of various ailments depending upon their particular properties.

Metals such as ^{57}cobalt(III) is used to detect tumor or cancer cells. The paramagnetic metals gadolinium(III), iron(III), and manganese(II) having the ability to alter the tissue relaxation times can produce contrast images important for MRI. The radioisotope 99Tc of technetium is the most used radioisotope agent for imaging purposes.

Also, Singh and Sharma (2018) show a table containing 23 metals and their complexes and the trade names too, used for the treatment of various diseases, few of them herein exemplified: *aluminum* (Al) under the form of hydroxide (Gaviscon) is used to treat heartburn and under the form of silicate (kaolin) used to treat diarrhea; *antimony* (Sb) under the form of sodium stibogluconate is used to treat leishmaniosis; *arsenic* (As) under the form of the organic compound melarsoprol is used to treat sleeping sickness; *bismuth* (Bi) under the form of bismuth complex is used to treat heartburn, diarrhea, and peptic ulcer; c*alcium* (Ca) under the form of carbonate is used to treat heartburn, peptic ulcer, and diarrhea; *copper* (Cu) as histidine complex is used to treat Menkes disease; *gallium* (Ga) as gallium(III) complex is used to treat cancer; *gold* (Au) as gold(III) complex or as gold(I) complex is used to treat cancer and arthritis, respectively; *iron* (Fe) as iron complex is used to treat anemia;

lithium (Li) as lithium carbonate is used to treat maniac depressive illness; *magnesium* (Mg) as magnesium sulfate (Epsom salt) or as magnesium hydroxide (milk of magnesia) is used to treat constipation and heartburn.

Also, Singh and Sharma (2018) provide interesting information on the use of some metals, such as As, Sb, Co, Cu, Au, Pt, Ru, and Se, and their complexes, against cancer involving chemotherapy and radiotherapy, as well as on the already known mechanism of actions of metals against various diseases and on the already known limitations of metals used in Medicine System.

Already in the present century, scientists had find out that metals such as Ag, Zn, Cu, Cd, Sn and Fe have microbicidal properties (see Sect. 7.5 in Chap. 7 of this book).

Metals are the active centers of the so-called metalloenzymes, a type of *metalloproteins* that make up about one-third of the known *macromolecules* formed of several amino acids, and it is assumed that the said dependence will reflect on the environment where cell life has emerged in the Hadean eon. Among all metalloproteins, *Fe metalloproteins*, particularly *Fe-S metalloproteins*, are supposed to be the most important and ubiquitous group in the organisms. By definition, enzymes are protein structures capable of acting as catalysts in biochemical processes, a catalyst being a compound capable of increasing the rate of a reaction although not being consumed by it.

Belmonte and Mansy (2016) in an excellent and current paper discuss the similarities between metals in ionic form, minerals, and biological enzyme catalysts, and how cell life could have harnessed the prebiotic metal complexes. The authors admit that the influence of metal ions on prebiotic chemistry may not be confined to mineral surfaces. Some protein enzymes of contemporary life coordinate metallo-*complexes* similar to the constituents of minerals, as is the case of *greigite* (Fe_3S_4), and the Fe_3S_4 and Fe_4S_4 clusters were found to be coordinated to several of the protein enzymes necessary to support life. Modern proteins coordinate metal ions other than Fe^{2+}, e.g., Ni^{2+} and Zn^{2+}. The so-called transition metals (with emphasis on V, W, Fe, Cu, Ni, Co, Cr, Mn, and Mo) have special relevance due to their redox activity and/or high electric charge density providing the polarity of the base protein of the *metalloprotein*. Many of these metals, in small amounts as trace metals, are required by the human body, for example, iron (Fe) is present in hemoglobin; copper (Cu) and manganese (Mn) are present in enzymes; and chromium (Cr) is a cofactor in the regulation of sugar levels. However, depending upon the concentrations, these and other metals may have detrimental health effects.

Also, metals emitted, for instance, from mining works, accumulate in the soil in surrounding areas, and the contaminated soil poses a hazard to human health, as the metals may be absorbed by vegetables grown in the contaminated soil, leach into underground water sources, or become airborne through wind-blown dust (Kumar et al. 2014). Humans may therefore be exposed to metals via *inhalation* and *ingestion*, as well as via *dermal absorption* through direct skin contact.

Some *metalloproteins* involved in electrowinning reactions may act, either as a reservoir, e.g., *ferritin* for Fe, or as carrier, e.g., *transferrin* for Fe. Iron (Fe) is the most abundant transition metal in the Earth's crust, and biologically it is the most important nutrient for most living organisms as it is the cofactor for many vital proteins and enzymes. Fe it is a most crucial element for growth and survival of almost all living organisms. Fe is essential to human life and health, since Fe-mediated reactions support the respiration process. The total Fe in the human body is about 3–4 g, and 2/3 of this value is located in the *erythrocytes*. Fe participates in various biological redox processes due to its interconversion between ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions.

Hemoglobin is a metalloprotein that contains iron (Fe) present in red blood cells or erythrocytes and allows the transport of O_2 by the circulatory system. It is a quaternary structure globular protein containing four polypeptide chains (globins) and one heme group attached to each of the globin chains. A healthy individual has 12 to 16 grams of *hemoglobin* in every 10 mL of blood. In mammals hemoglobin makes up about 96% of the red blood cells' dry content by weight, and around 35% of the total content (water included).

The Fe function is to absorb and transport the O_2 in the blood and release it into the tissues. Fe atoms bind to O_2 reversibly. The *heme group* consists of a molecule called *protoporphyrin* which coordinates an atom of Fe. *Hemoglobin* has an oxygen-bonding capacity of 1.34 mL of O_2/g. Anemia is a disease that, as a rule, is due to Fe deficiency in blood, and according to WHO, it is easily diagnosed through blood analysis. Women with hemoglobin levels less than 12 g/dL and men with levels less than 13 g/dL are said to be anemic. Anemia symptoms are not specific. According to the AWGP (Anemia Working Group Portugal), based on an epidemiological study named Empire published in 2016 and carried out in a sample of 8000 individuals measuring hemoglobin and ferritin, this being a parameter that measures Fe reserves in the organism, the anemia prevalence in Portugal was estimated at 20%.

Zinc (Zn) is another metal that plays an important role both in the activity of many vital enzymes and in protein biosynthesis and its uses inside the body. In the presence of Zn, the body produces lactic acid as well as the enzymes *alkaline phosphatase*, *carbonic anhydrase*, and *carboxypeptidase*. *Zinc* deficiency significantly inhibits many biological processes and is responsible for growth retardation.

Other metals are involved in the formation of important *enzymes*: *ascorbic acid oxidase* (*copper*, Cu), *cytochrome* (*iron*, Fe), *cytochrome oxidase* (*copper*, Cu), *glutamate mutase* (*cobalt*, Co), *glutathione peroxidase* (*selenium*, Se), *urease* (*nickel*, Ni), and *xanthine oxidase* (*molybdenum*, Mo).

Phosphotransferase is a metalloenzyme that has *magnesium* (Mg), and *arginase* is another *manganese-containing metalloenzyme* (Mn).

In the particular case of selenium (Se), this mineral integrates the structure of several essential substances for the human organism, called *selenoproteins*. About 25 different *selenoproteins* are known, 6 (six) of them being involved in the functioning of the thyroid gland so important for metabolism. Se deficiency can cause imbalances in the normal functioning of the thyroid gland, called *hypothyroidism*, if the gland is hypoactive, and *hyperthyroidism*, if the gland is overactive. *Selenoproteins* have other functions in the body, being involved in male fertility, immune system response, and antioxidant defense.

As a result of soil characteristics and dietary habits, about 20% of the European population does not get the recommended daily amount of Se, estimated at 55 μg/day. Vegetarians, vegans, and those who do not consume fish and shellfish show a lack of Se.

It is now recognized that the Portuguese population consumes low levels of Se, even below the recommended value, situation explained by the low levels of Se present in agricultural soils and cereals consumed. Deficiency of Se can be offset by the ingestion of mineral supplements that contain Se.

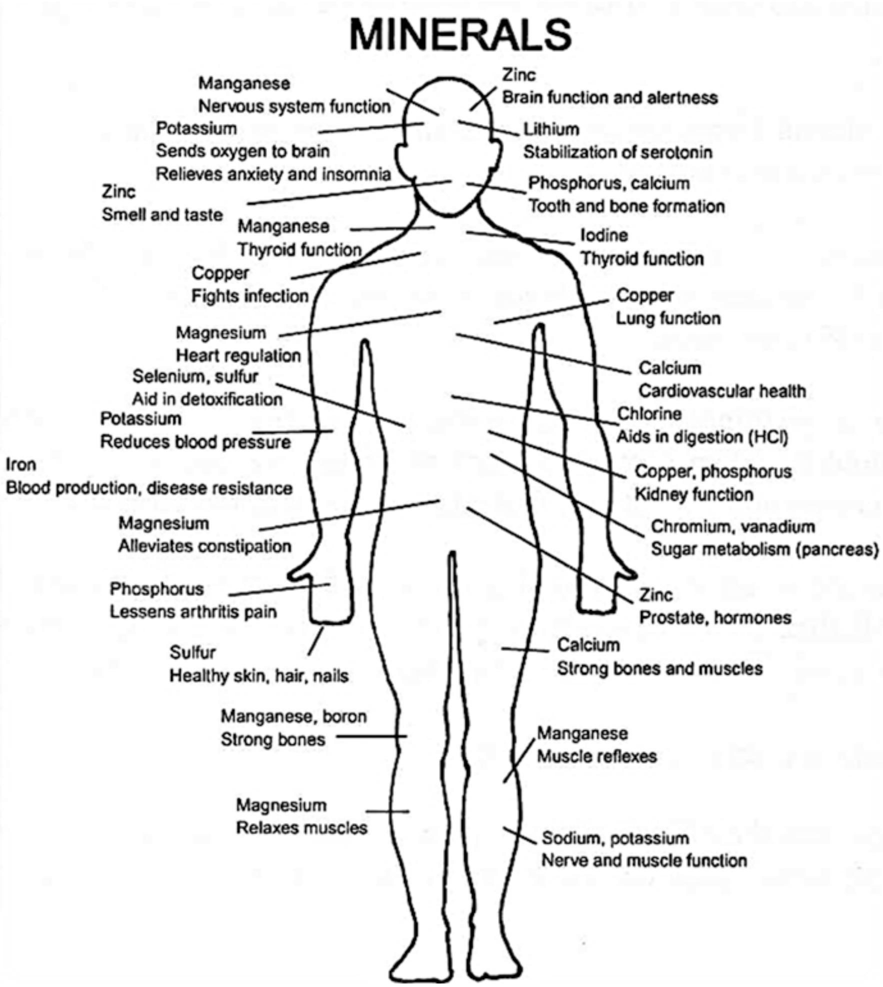


Fig. 4.2 Brief indication of some beneficial functions of metals and metalloids on human health. (Source: https://www.inlifehealthcare.com/2015/03/02/7-essential-minerals-natural-food-sources/)

The purpose of the enzymes is to accelerate or catalyze the numerous chemical reactions that take place in the human body. There are a large number of specific enzymes that play important roles in physiological processes (digestion, nerve conduction, synthesis of hormones, etc.).

Figure 4.2 shows the beneficial functions on the human health of major and trace elements, metals, and metalloids.

4.4 Bio-Essential Minerals in the Elemental Form

Minerals and the human body are chemical systems having in common most of the chemical elements contained in the periodic table (with the exception of the noble or rare gases and the so-called transuranium or artificial elements), and they may interact positively or negatively, in terms of human health.

Figure 4.3 shows the periodic table (source BSG-UK) with elements considered essential or vital for human health, elements considered or recognized as being toxic or undesirable, and elements awaiting demonstration of possible essentiality for the living beings.

The periodic table of the chemical elements including the aforementioned elements, a table also known as Mendeleev's table, in honor of the Russian chemist Dimitri Mendeleev, who in 1869 published a chart where the chemical elements were arranged in horizontal lines or rows also called periods, in ascending order of their atomic weight, and in vertical columns also called groups, including chemical elements with similar properties.

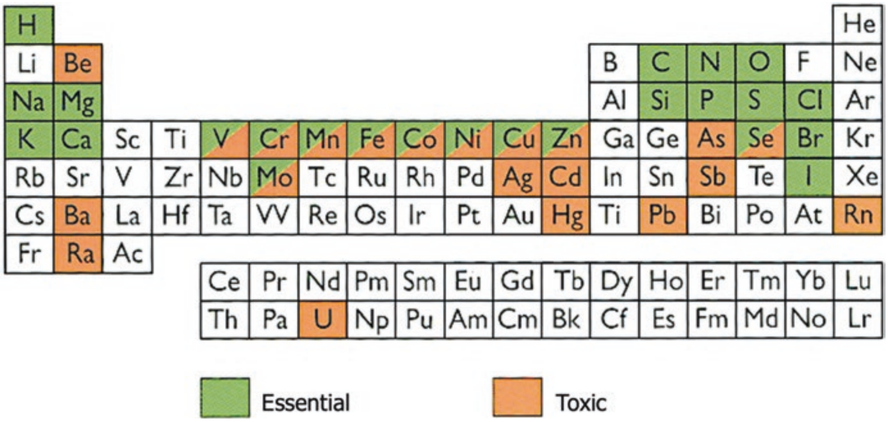


Fig. 4.3 The periodic table showing chemical elements that are essential (in green), toxic (in orange), and both essential and toxic (green/orange). In the table there are only 103 elements. Currently, the periodic table comprises 118 elements, all of which have an atomic number higher than that of uranium (U) which is 92 (source BGS). The elements in the periodic table are distributed in 7 rows called periods and in 18 columns called groups

Mendeleev's table consists of 7 rows or periods and 18 columns or groups, and there were empty positions that Mendeleev assigned to hitherto unknown elements but which, based on the properties of the familiar elements already known, made it possible to predict the properties of these unknowns.

The periodic table developed by Mendeleev after gathering all the information that existed at that time about the known elements, when many of the natural elements were still unknown, was recognized so remarkably that it deserved from the scientific community the attribution of its name (Mendelevius) to the element of atomic number 101. In the table, the natural elements are numbered 98, including the so-called noble or rare gases: helium, neon, argon, krypton, xenon, and radon. Artificial elements in number of 20 are produced by the bombardment of atomic nuclei with protons or smaller nuclei.

Each element is represented in the periodic table within a square in the middle of which is the chemical symbol of the element, for example Mg, and underneath the extended name of the same element (Magnesium) and below the atomic mass 24.31 and in the upper left corner the atomic number 12.

We had commemorated the 150th anniversary of the periodic table in 2019, the International Year of the Periodic Table. The periodic table is not an aleatory collection of individuals or elements, in it there is a hidden order. There are relationships between all elements, based on the atomic structure, for instance, between O and S and between C and Si.

The great advances of science and the well-being of humanity are due to chemistry, with reflexes in all scientific areas, particularly in Medicine, Physics, Geology, and Biology. For instance, according to Peter Atkins, Professor of Chemistry at the University of Oxford, England, the greatest contribution of Chemistry to Medicine and human well-being would have been the discovery of anesthesia. Almost everything man uses is synthetic, produced by chemistry, fabrics, building materials, medicines, etc., but we must not forget that to make them man resorted to natural materials, many of them minerals.

Any chemical element, macro- or microelement, performs specific biological functions in relation to human health. Based on the information obtained from Nieboer and Sanford (1984), Wada (2004), Lindh (2005), Combs (2005), Sitalakshmi and Kumar (2014), Fairweather-Tait and Cashman (2015), and Al-Fartusie and Mohssan (2017), the biological functions and impacts, overload or deficiency, on nutrition of some chemical elements or minerals, almost all metals and metalloids, and considered essential for human health, are put forward in a synthetic way. With regard to trace elements which are micronutrients, they are required in the diet in very small amounts. Although they are required only in small amounts, they are critical for both health and disease. Sitalakshmi and Kumar (2014) present an interesting review on trace element dietary sources, recommended dietary intake, deficiency states, and hazards of excessive consumption.

The handbook of the *Nutritionally Essential Mineral Elements* – edited by O'Dell and Sunde RA and issued in 1997 by Marcel Dekkery Inc., New York – is a milestone on the subject of the interrelations between minerals and human health and disease.

Table 4.2 Typical weight contents (in %) of the chemical elements, the most important existent in the human body (Lindh 2005)

Element	% in weight	Element	% in weight
Oxygen	65.0	Magnesium	0.50
Carbon	18.0	Potassium	0.34
Hydrogen	10.0	Sulfur	0.26
Nitrogen	3.0	Sodium	0.14
Calcium	1.4	Chlorine	0.14
Phosphorus	1.0		

Table 4.3 Typical levels (in grams and milligrams) of some of the nutritionally essential chemical elements (minerals) in the human body (Lindh 2005)

Element	Typical content
Calcium	1000 g
Phosphorus	700 g
Potassium	110–150 g
Magnesium	20–28 g
Sodium	1.3 g
Zinc	2–2.5 g
Copper	120 mg
Selenium	20 mg

H, C, N, O, Na, Mg, Ca, P, S, Cl, K, Mn, Fe, Cu, and Zn are being considered worldwide as essential elements for all animals and plants.

H, O, C, and N make up more than 96% of the weight of the human body, which is why they are called major elements, their concentration being expressed as $g.kg^{-1}$.

Na, K, Ca, Mg, P, S, and Cl make up 3.78% of the weight of the human body, which is why they are called minor elements or minor minerals, and their concentration being expressed as $mg.kg^{-1}$.

Table 4.2 shows the typical weight contents (% in weight) of the most important chemical elements existing in the human body.

Fe, Zn, Cu, Mn, F, Mo, Se, Cr, Si, and I are called trace elements or trace minerals, and the respective amounts are expressed in $\mu g.kg^{-1}$.

Table 4.3 shows the typical levels (in grams and milligrams) of some of the nutritionally essential chemical elements (minerals) in the human body (Lindh 2005).

In turn Table 4.4 shows the abundance in terms of mass (in $\mu g.kg^{-1}$) of trace elements or oligoelements essential for the human body (Lindh 2005).

The World Health Organization (WHO) in 2002 considered the following trace elements or trace minerals Fe, Zn, Cu, Cr, I, Co, Mo, and Se essential for human health.

According to Lindh (2005), an element is bio-essential when:

1. It is present in living tissues in relatively constant concentration.
2. It causes similar structural and physiological anomalies in several species when removed from their organisms; these anomalies are prevented or cured by the application of nutritional supplements containing this element.

Table 4.4 Abundance in terms of mass (in $\mu g.kg^{-1}$) of trace elements or trace minerals essential for the human body (Lindh 2005)

Element	Weight fraction	Element	Weight fraction
Silicon	260	Manganese	0.17
Iron	60	Nickel	0.14
Fluorine	37	Selenium	0.11
Zinc	33	Vanadium	0.11
Bromine	2.9	Chromium	0.094
Copper	1.0	Cobalt	0.021
Arsenic	0.26	Molybdenum	0.008
Tin	0.24	Lithium	0.009
Iodine	0.19	Tungsten	0.008

For the World Health Organization (WHO), an element is considered essential to an organism when: "Reducing its exposure below a certain threshold consistently results in the reduction of a physiologically important function, or when the element being an integral part of the body's structure a vital function in this same organism."

Combs (2005) considered 16 elements to be essential for good human health, performing 5 general physiological functions:

1. Structure of bones and cartilages (Ca, P, Mg, and F).
2. Water and electrolyte balance (Na, K, and Cl).
3. Metabolic catalysis (Zn, Cu, Se, Mg, and Mo).
4. Oxygen binding and respiration (Fe).
5. Hormone effects (I and Cr).

Combs (2005) classified the essential chemical elements into two major groups:

1. Macronutrients or macrominerals (Ca, P, Mg, Na, K, and Cl) required in large quantities expressed in the diets in grams per kilogram (g/kg);
2. Micronutrients or microminerals (Fe, Cu, Zn, I, Se, Mn, Mo, Cr, F, and Co) required in much smaller quantities expressed in micrograms per kilogram (kg) or in milligrams per kilogram (mg/kg).

According to Dunn and Irvine (1993), among the total number of 30 essential elements, some are considered essential for all living beings (C, Co, Cu, Fe, H, K, Li, Mg, Mn, Mo, N, P, S, and Zn), and others are essential for most living beings (Al, As, B, Br, Ca, Cd, Cl, Cr, F, I, Na, and Ni).

Si, V, Co, Mo, and I are other *trace elements* essential to some classes of animals and plants, and B, F, Cr, Br, Li, Al, Ni, Sr, and Ba are also essential for some classes of animals and plants, and like the aforementioned elements, their absorption is via food, water, soil, and air. Other *trace elements*, such as, Cd, Hg, Pb, Ni, Sb, Sn, Ti, and Be, are considered nonessential.

Various biological classifications of trace elements have been proposed by several authors (e.g., Prashanth et al. (2015)).

Frieden had considered three categories of trace elements, based on the amount found in tissues: microelements (B, Co, Cu, Fe, I, Mn, Mo, and Zn), trace elements (Cr, Ni, F, Se, and V), and ultratracelements (Br, Li, Si, Sn, and Ti).

Prashanth et al. (2015) had considered five categories or groups of chemical elements which are important in terms of human health:

1. Group I (C, H, O, and N): the basic constituents of macromolecules such as carbohydrates, proteins, and lipids;
2. Group II (Na, K, Cl, Ca, P, Mg, and S): nutritionally important minerals, called principal and macoelements, and the daily requirement for an adult human is above 100 mg/day;
3. Group III (essential trace elements, Cu, Fe, Zn, Cr, Co, I, Mo, and Se);
4. Group IV (their role is not clear, and they may be essential, Cd, Ni, Si, Sn, V, and Al);
5. Group V (nonessential, their presence may produce toxicity, Hg, Pb, and Au).

Wada (2004) produced an excellent article entitled "What are Trace Elements: Their Deficiency and Excess states" that discloses interesting information on trace elements concept, physiological functions, symptoms of deficiency, and symptoms of excess of trace elements. Also, according to Sitalakshmi and Kumar (2014), trace elements or trace minerals constitute 0.005% of the total human body weight, and it is difficult to do their precise estimation in serum, leucocytes, lymphocytes, hair, and urine since they are present in minute quantities.

Atomic absorption spectrophotometry is the most used technique in trace element estimation. It is estimated that more than 3 billion of the world's population are affected by micronutrient (trace elements + vitamins) deficiencies. The major causes of trace element deficiencies are as follows: inadequate supply, congenital metabolic disorders, inadequate intake, iatrogenic causes, and metabolic diseases.

Fairweather-Tait and Cashman (2015) produced another excellent article entitled "Minerals and Trace Elements" that deals with the physiological functions of minerals and trace elements, with the health disorders caused by their deficiency and toxicity, and with the respective signs and symptoms. Also, in regard to the physiological effects and clinical practices related to trace elements deficiency in infants and children and in aged people, the articles in the same journal by Kodama (2004) and Itokawa (2004), respectively, disclose very interesting information.

Fukuda et al. (2004), Kihira (2004), and Sinha (2014), all expend relevant information relating trace elements with cancer as well as with nervous and mental diseases, respectively.

In addition to the chemical elements, macronutrients or micronutrients of inorganic origin, the so-called macrominerals or microminerals, respectively, and which are essential to life, foods, particularly the so-called functional foods contain organic compounds of organic origin that are equally essential for good health, such as vitamins, folic acid found in cereals, and omega-3-type unsaturated fatty acids in fish.

Calcium (Ca) and phosphorus (P) are the most abundant bio-essential chemical elements in the human body, which combined as calcium phosphate and in the form of the *biomineral* named *hydroxyapatite*, $Ca_{10}[PO_4]_6(OH)_2$, participate in the composition of the bones of the skeleton that supports the muscles and protect the vital organs. *Brushite*, $CaHPO_42H_2O$, and *whitlockite*, $(Ca,Mg)_3[PO_4]_2$, are other *biominerals* being identified in the bone. In addition to the minerals that participate in the composition of the bones, collagen fibers are arranged in layers and a gel or protein glue sugar (the *glycoproteins*) participates too.

In the human body, there are 206 bones, some larger (the femur in the thigh which is about 50 cm in an adult and humerus in the arm which is about 36 cm in an adult), while others are smaller as is the case of *stirrup bone* of the inner ear (measuring 3.5 mm which is the smallest bone in the human body). Only the hands and feet contain 106 bones, that is, more than half of the bones of the body.

As for the structure of the bones, there is usually a compact outer layer (*cortical bone*) that confers rigidity and a flexible spongy inner zone (*trabecular bone*), known as red bone marrow, where the production of blood cells and the exchange of Ca and other minerals such as Mg, Sr, Na, and Si occur.

Bone formation continues until 18–20 years of age, at which time 90% of bones are formed. The remaining 10% are formed up to the age of 30, after which the bones enter into continuous loss of bone mass, increasing porosity, and, consequently, brittleness, a situation that can result in very severe fractures as a rule of the neck of the femur, the basin, the spine, and the wrist.

It is now widely accepted that lifestyle, diet, and physical exercise in particular contribute to the preservation of bone integrity. There is also clinical evidence that recent medications from the *bisphosphonate* group, such as *alendronate* tablets, in the form of *alendronate sodium trihydrate*, associated with *cholecalciferol* (vitamin D_3), prevent bone fragilization, clinically called *osteoporosis*.

Ca *Calcium* is an essential mineral for the development and maintenance of healthy bones and teeth; calcium participates in muscle contraction and nerve transmission and helps reduce the risk of osteoporosis, a medical disease with many ramifications.

Recently, Schweser and Crist (2017) have discussed the developments on osteoporosis along the past 5 years based on the literature being produced.

Prior to modern imaging, the diagnosis was often made only after a person sustained a fragility fracture. These days dual energy X-ray absorption (DXA) allows the diagnosis prior to a fracture occurring and gave providers the chance to initiate appropriate treatment. DXA scans allow the measurement of the bone density, as X-ray absorption is directly related to calcium content within the tissues (Kanis et al. 2014).

The average content of Ca in the human body is 1200 g, body weighing 70 kg, and 99% of which is in the skeleton. Ca RDD (recommended daily dose) in healthy adults regulates between 1000 and 1200 mg/day, depending on age and gender.

Calcium and vitamin D supplementations still are a staple for the treatment of osteoporosis. There is some variation in the recommended daily values depending on the source, but the range for vitamin D is typically 600–800 international units per day (IU/d) with Ca ranging 1000–1200 mg/day for men and women over 50

(IMC to Review Dietary Reference Intakes for Vitamin D, Calcium, 2011; Cosman et al. 2014).

The management and understanding of osteoporosis had made significant advances over the years, but there is still a long way to go. The disease crosses many medical specialties, and bone health remains an area of medicine still with many unanswered questions (Schweser and Crist 2017).

The current diagnosis of osteoporosis is based on the use of DXA scans which allow the measurement of the bone mineral density. The diagnosis, expressed by the T-score is based upon the standard deviation from the bone density of a normal 30-year-old woman. A standard deviation (SD) around 1 means normal bone density, where as a standard deviation (SD) of 2.5 or greater below normal confirms osteoporosis (Lorentzon and Cummings 2015).

P *Phosphorus* is an essential mineral for life and health, since it is required by every cell in the human body for its normal function. The majority of P in the body is found as phosphate (PO_4). As phosphate it is a structural component of DNA, RNA, and ATP molecules.

Nucleic acids DNA and RNA are long chains of phosphate-containing molecules which are responsible for the storage and transmission of genetic information. Living cells use phosphate to transport cellular energy in the form of adenosine triphosphate (ATP) and creatine phosphate. Also, P is a basic constituent of the phospholipids that form all cell membranes, which are made from phospholipids matrix and proteins, typically in the form of a bilayer. Phospholipids (e.g., phosphatidylcholine) are major structural components of cell membranes. P also helps to maintain normal acid-base balance by acting as one of the body's most important buffers.

Phosphorus together with calcium in the form of calcium phosphate called hydroxyapatite helps to develop and maintain strong bones and teeth; favors the metabolism of other nutrients; its average content in the human body is 780 g (body weighing 70 kg) and about 85% is in the bones.

Inadequate phosphorus intake results in abnormally low serum phosphate levels called *hypophosphatemia* identified by loss of appetite, anemia, muscle weakness, bone pain, osteomalacia, and increased susceptibility to infection. Since P is so widespread in food, dietary P deficiency is a biomarker of starvation or anorexia.

S *Sulfur* is required for the muscle and hair proteins; its deficiency results in the degeneration of collagen, cartilage, ligaments, and tendons; the average content in the human body is 140 g, body weighing 70 kg; it is well recognized that sulfur in the form of glucosamine sulfate and chondroitin sulfate which contain biologically active compounds called glycosaminoglycans which are also present in the human cartilage and have the ability to collect water which gives them the actions of lubricant and buffer; hence the sulfates mentioned are used in the treatment of worn articular cartilage.

Sulfur can damage the internal enzyme systems. Sulfur-bearing substances can cause neurological effects and behavioral changes, disturbance of blood circulation, disturbance of hormonal metabolism, and changes on eyes and eyesight. Sulfur investigations conducted in recent years have shown to play an important role in treating arthritis which is an inflammatory state of joints, usually associated with pain, swelling, and stiffness. Arthritis can occur in several forms: bacterial arthritis, rheumatoid arthritis, and osteoporosis. It is in this latter pathology that experience has shown the positive effect of S in the form of glucosamine sulfate and chondroitin sulfate supplements that aid in the production of new cartilage replacing the degenerate cartilage.

According to Carbajo and Maraver (2016), S in the form of H_2S (hydrogen sulfide) occurs in sulfurous waters widely used in *balneotherapy*, and its absorption, for example, through the skin, can promote arterial vasodilation and blood circulation and regulate blood pressure and, therefore, can solve cardiovascular and ischemic problems.

In balneology H_2S can also be absorbed by respiratory and digestive tract. According to the aforementioned authors, several scientific articles mention the influence of H_2S on musculoskeletal inflammatory diseases, in the case of osteoarthritis (OA). In the case of the topical use of *peloids*, H_2S is part of the liquid phase, sulfurous water, themselves.

According to Vela-Anero et al. (2018), the progressive destruction of cartilage leading to the malfunctioning of the joints is one of the most prominent facts of the pathology osteoarthritis (OA) that has no cure and, at present, the treatments are mainly symptomatic, and not impediment of the progress of the disease. The tiny gaseous H_2S molecule has been shown to be able to prevent cartilage degradation and also to exert anti-inflammatory effects in the case of OA, which led the authors to perform in vitro tests applied on the knee of rodents through the intra-articular administration of a compound (200 μM GYY4137 in 50 μl saline) producing H_2S.

The results of the tests allowed to demonstrate not only the reduction of cartilage destruction but also the reduction of pain in the animals tested, leading the authors to confirm the potential of H_2S in the pharmacological treatment of OA.

Sulfurous mineral-medicinal waters containing H_2S occur and are used in many thermal balnearies of central and northern Portugal.

Mg *Magnesium* is another bio-essential element. In humans, Mg is mainly found (50–60%) in the bones and also in the cells of other tissues, being more concentrated in the cells of the muscles and the blood.

Magnesium promotes the activation of more than 300 different enzymatic processes; helps in the functioning of nerves and muscles; its deficiency causes cramps; intervenes in maintaining the structure of bones; and regulates the passage of chemical elements through cell membranes. The average content of Mg in an human body weighing 70 kg is 25 g; about 60% of the body Mg occurs in the skeleton and the remainder occurs in cells that require energy for metabolism and cell replication. Mg DDR in healthy adults regulates between 310 are 420 mg/day.

The Mg^{2+} cation is essentially an intracellular cation; 31% is within the cells, 1% is in the extracellular space, and 67% is as a constituent element of the bone.

Magnesium plays an important role in the activation of enzymes involved in energy production and also has a regulatory function of the intracellular metabolism of calcium (Ca), phosphorus (P), and sodium (Na). Mg also interferes with the transmission and neuromuscular activity, acting as a relaxant in muscle contraction; promotes the health of the cardiovascular system contributing to the prevention of strokes; and prevents the formation of "stone" in the kidneys and gallbladder.

The absorption of Mg is made, as for most of the elements, essentially in the small intestine, being almost completely eliminated by the renal route.

Magnesium deficiency is attributed to several diseases: circulatory, cardiac, osteoporosis, diabetes, gastritis, arthrosis and arthritis, and renal diseases, among others. Some symptoms of Mg deficiency are tremors, muscle spasms, apathy, weakness, cramps, nausea, and vomiting. Mg deficiency can be overcome through the use of certain drugs, such as the drug called *Magnesone* (magnesium pidolate) which is taken as an oral solution. As with other chemicals when used in excessive amounts, excessive concentrations of Mg in the blood can lead to health problems, such as hypotension, arrhythmia, and respiratory failure.

The main sources of Mg are nuts, whole grains, legumes, and dark-green leafy vegetables.

Na *Sodium* content in the human body of this macronutrient or macromineral corresponds to about 2% of the total of minerals in the body. Most of the sodium (Na) is in the blood, bone, and extracellular fluid (30–45%).

Na maintains the hydroelectrolyte balance and controls blood pressure, muscle contraction, and nerve conduction; the average content in the human body is 100 g, body weighing 70 kg.

In animal cells the level of Na^+ concentration in the intracellular fluid is about ten times lower than the level of concentration of the same ion in the extracellular fluid. In contrast, the level of K^+ concentration in the intracellular fluid is about 30 times higher than the concentration level of the same ion in the extracellular fluid. The net result of the said gradient is that, in a resting cell, the K^+ is pumped into the cell, while the Na^+ is expelled out, and, in order to maintain the concentration gradients, energy must necessarily be consumed, which is achieved through ATP hydrolysis (adenosine triphosphate).

The kidneys control the levels of Na in our body. If we have too much Na and our kidneys cannot get rid of it, Na builds up in our blood and can lead to high blood pressure and consequently to health problems.

Sodium is essential for nerve transmission, muscle contraction, and fluid balance. Na is also essential for acid/base balance and for regulating blood pressure. The excess of Na in the human body is very frequent and can lead to hypertension. In turn, Na deficiency is rarer but can lead to a decrease in blood pressure, elevated heart rate, fatigue, hypotonia, and hypotension. Na is ingested and incorporated through food and beverages and is eliminated through the sweat and Na that we ingest comes from the cooking salt that is added to the foods we consume.

Sodium is the fundamental constituent of the salt (NaCl) of rock salt deposits and of salt pans where it is currently "manufactured" to be use in seasoning foods, which occur in several regions of the world. This type of salt, whose health benefits have long been recognized, provides when other than life-sustaining elements such as chlorine, potassium, magnesium, iodine, and others are ingested in addition to Na.

The salt of rock salt deposits has also been used in the treatment of respiratory diseases. Effectively, the saline aerosols which are formed by vaporization in rock salt mines, as happens at the Royal Mine of Wieliczka, Poland, an impressive and unimaginable set of chambers, galleries and underground chapels carved out of rock salt. The Royal Mine of Wieliczka is part of UNESCO's Natural and Cultural Heritage and has been used for the aforementioned type of treatment. In the past a sanatorium had been installed and functioned in this mine.

Also, there is the practice of using blocks of salt from the said mine, in case well dimensioned cavities are built in the core of the blocks to allow the adaptation of electric lamps. Due to hydration caused by the humidity of the ambient air, a slow dissolution of the salt occurs, and the heat of the lamp promotes the volatilization of the ions present in the salt, such as Na^+, K^+, Mg^{2+}, I^-, Cl^-, and Br^-. Electric lamps based on the blocks of rock salt from the Himalayan range are also marketed for the abovementioned purposes.

Salt can also be used in the composition of body scrubs for skin exfoliation treatments that remove dead cells and improve blood circulation.

K *Potassium* is the fourth most abundant chemical element or mineral in the human body after Ca, P, and Mg, contributing to lower blood pressure and preventing vascular accidents. The human body needs K to work normally; it is critical to the functioning of nerve and muscle cells including those of the heart.

Potassium (K) helps to move nutrients into the cells and waste products out of the cells. A diet rich in K helps to offset some of Na harmful effects on blood pressure. Blood potassium level is normally 3.6–5.2 millimoles/liter. K regulates heart rate, maintains fluid balance, and aids in muscle contraction.

The human body weighing 70 kg contains in average 125 g grams of K, which in contrast to Na exists especially in intracellular fluid. Potassium controls the acid-base balance. The deficiency of K is called *hypokalemia*, a potentially fatal condition, while the excess is called *hyperkalemia*.

Hypokalemia can cause weak muscles, abnormal heart rhythms, and a slight rise in blood pressure. Low K is associated with heart disease, stroke, arthritis, cancer, digestive disorders. For people with low K, doctors sometimes recommend improved diets or potassium supplements. *Hyperkalemia* can cause abnormal and dangerous heart rhythms.

Most minor and trace minerals or trace elements are also fundamental or essential to human health.

I *Iodine* is an example of a minor or trace mineral that is essential for the proper development of the central nervous system and necessary for the proper performance of thyroid hormones that control important functions of the body, such as temperature, growth, reproduction, etc.

Iodine dietary deficiency and excess of iodine promote the onset of disorders in the thyroid gland, expressed, for example, by the disease called goiter. Most iodine exists in marine sediment, marine algae, and saltwater fish. According to the WHO (World Health Organization), iodine deficiency disorders (IDD) have been identified in 130 countries, and 2.2 billion people, or approximately 38% of the world's population, live in iodine-deficient regions.

The body of a healthy person (weighing about 70 kg) contains 15–20 mg of iodine, the minimum daily requirement is 100–150 µg, and almost all of it is taken up by the thyroid gland and used to synthetize the thyroid hormone, while the remaining iodine (about 100–200 µg/L) is excreted in the urine (Iitaka 2004).

The decrease in thyroid hormone leads to an increase in the thyroid-stimulating hormone (TSH) resulting in the development of *goiter*, the disease that affects 740 million people worldwide, accounting for 13% of the world's total population. *Cretinism*, a neurological disorder, is another disease due to iodine deficiency.

Vitti et al. (2001) provided information on iodine deficiency disorders in Europe (97 million people are reported to have goiter due to iodine insufficiency).

The WHO, UNICEF, and the ICCIDD (International Council for Control of Iodine Deficiency Disorders) are actively attempting to eradicate IDD; since iodine deficiency can be prevented by iodine supplementation, commitment and motivation of countries' government are essential to eliminate iodine deficiency disorder (IDD).

In Portugal, about 1 million people, particularly women, have health problems (cancer included) with the thyroid gland due to iodine deficiency in the diet, which are reflected in metabolic and cardiovascular functioning. Iodine deficiency can cause the disease called *goiter*, expressed by the abnormal growth of the thyroid gland. In Portugal it is in the interior regions of the country that the *iodine* deficiency in people is more noticeable.

The highest concentrations of iodine are present in seawater, algae, and organic matter-rich soils located in coastal areas. The main source of iodine is food, particularly food from the sea, vegetables, meat, and eggs. At present, in developed countries, the most important sources of iodine other than natural sources are milk, butter, and cheese, due to the iodine additives introduced into animal feed.

The Directorate-General for Health, concerned about the lack of iodine in the Portuguese population, has decided to elaborate a small book "Iodine: Importance for Health and the Role of Food" in which it explains the daily doses of iodine recommended and the best forms of iodine. A daily dose of 250 µg (micrograms) of iodine to pregnant women and 150 µg (micrograms) of iodine to breastfeeding women are recommended. A study carried out in 2010 with a sample of 3631 pregnant women in 17 Portuguese inland, coastal, and autonomous maternity hospitals, showed that 83% of the women had iodine values lower than those recommended.

There is an indication that iodine deficiency in pregnant women may be associated with congenital malformations and premature births. In turn, in children, iodine deficiency may be associated with mental retardation. Diets based on fish, other seafood, vegetables, and dairy products are recommended as well as a supplement of potassium iodide.

The so-called *iodized salt* with 20–40 mg of *iodine* per pound of salt is an effective supplement indicated as a substitute for regular salt for anyone who has iodine deficiency. There is information that “with 2 grams of iodized salt per day and a dose of cod you can get the recommended daily dose of iodine.”

Si *Silicon* is another chemical element, effectively a metalloid, which is also bio-essential.

Silicon (Si) is an abundant nonmetallic trace element in nature and has been proved to be essential for normal bone growth, skin integrity, and flexible joints. The main source of Si for humans is the diet, from solid foods and from water. The human body contains approximately 7 g of Si, which is present in various tissues and body fluids. In tissues, it is usually bound to glycoproteins such as cartilage, whereas in blood fluids, it is almost entirely found as free orthosilicic acid.

After oxygen (O), silicon (Si) is the most abundant element making 28% of the terrestrial crust, where it occurs in the form of silicates combined with oxygen, sharing with it all or part of the four electrons of its electronic external layer. Silicon is released from silicates during weathering processes, and it is also released under water during volcanic activity. Very rarely does silicon occur in free form in nature, and when such happens in aqueous solutions it occurs as ortho-silicic acid, H_4SiO_4 or $Si(OH)_4$.

In humans, Si occurs in minute amounts, approximately 0.004%, playing an important role in the vascular, nervous, and respiratory systems and is present in the bones, joints, tendons, and skin. Silicon is a precious fortifier of elastic tissues and is relevant for the reconstruction of cutaneous tissues and for the defense of connective tissue.

Today Si is known as the “beauty mineral,” being essential for the smoothness and firmness of the skin, for the vigor of the hair, for the strengthening of the enamel of the teeth, and also for the resistance of the nails. In organic form, organic silicon is a stimulator of cellular regeneration. Silicon is required for the synthesis of *elastin* and *collagen*. The aorta contains the highest amount of *elastin* and *silicon*.

Silicon is found in foods such as rice, oats, and wheat, and also in water, particularly in the so-called silicate-rich water.

The biological requirement of Si was first demonstrated by Carlisle (1972) and Schwartz and Milne (1972), in experiments with rats and chickens, respectively, being fed with Si-deficient diets, and skeletal deformations did happen, as well as poorly formed joints due to decreased cartilage content.

According to Jugdaohsingh (2007), accumulated evidence over the last 30 years strongly suggest that dietary silicon is beneficial to the bone and connective tissue health. The author also mentions that strong positive correlations between dietary Si intake and bone mineral density have been recently found in the US and UK cohorts. The major and most important source of Si is diet (solid food and drinking water). Drinking water and other fluids like beer provide the most readily bioavailable source of Si in the diet, since Si is principally present as $Si(OH)_4$ (Bellia et al. 1994).

Dietary intake of Si is between 20 and 50 mg/day for most Western populations, but higher intakes (140–204 mg/day) have been reported in China and India where plant-based foods may form a more predominant part of the diet (Jugdaohsingh et al. 2002; National Academy of Sciences, 2001).

Recently Farooq and Dietz (2015) wrote an article entitled “Silicon as versatile player in plant and human biology: Overlooked and poorly understood” that is a review aiming to provide a broad perspective on Si as important trace element for plant and human nutrition and to define research fields for interdisciplinary research. Despite the significant empiric knowledge on the pivotal role of Si in the plants’ growth and development, the essentiality of Si still remains enigmatic.

Se *Selenium* has been recognized as an essential element for all life forms, mammals included. In nature selenium accompanies sulfides.

Se is a strong antioxidant chemical element that avoids or reduces the harmful effects caused by oxidation, responsible for the release of the so-called free radicals, and as such, responsible for cell aging too; is vital for the formation of dozens of *selenoproteins*, some of which are involved in the functioning of the immune system that is compromised by selenium deficiency or deficiency.

The selenium content in the adult human body varies between 10 and 20 mg. Selenium absorption from the diet is very efficient – much of it is in the form of selenomethionine or selenocysteine. Commercial Se supplements in the form of selenite or selenate are well absorbed, and all Se species in the diet will eventually be converted to selenophosphate, which is the precursor of selenocysteine (Shenkin 2008).

Selenium when present in the multivitamin and multimineral supplements, due to its anti-inflammatory effect, seems to contribute to the relief of the pain of rheumatoid arthritis. Studies have shown that selenium levels are lower in patients with rheumatoid arthritis. In addition to the anti-inflammatory properties, selenium is also attributed antioxidant and antiviral properties.

Selenate (Se^{6+}) and *selenite* (Se^{4+}) are the main inorganic forms of selenium present in mineral supplements and mineral water consumed, being absorbed in the intestinal tract and then in *selenite* form (Se^{2-}) biologically active. And, the main organic forms of selenium present in plant and animal food are *selenomethionine* and *selenocysteine* that participate in the so-called selenoproteins.

In human health Se is required in trace amounts but plays a central role in the synthesis of antioxidant selenoproteins such as glutathione peroxidase (GPx) for the protection against oxidative stress (Tapiero et al. 2003). Selenium is a constituent of enzyme glutathione peroxidase that is produced by the human body and is used to protect the cells and cell membranes from free radicals (aggressive molecules produced in the body by various biological processes, namely, inflammation) that damage the tissues. It also contributes to the functioning of the immune system (Beck 2001) and normal growth and development (Biri et al. 2007).

Selenium deficiency is attributed to neurodegenerative pathologies, such as Parkinson’s and Alzheimer’s disease, cardiovascular pathologies, and the weakening of immune function.

Li et al. (2012) disclose interesting information on the medical geology of arsenic, selenium, and thallium in China. In the case of selenium, the impacts on human health of selenium deficiency and excess are fairly described, and Se sources and distribution being identified. There are regions in China that are characterized by very low and others by very high Se concentrations, explaining both endemic Se deficiency and selenosis.

Many cases of Kashin-Beck disease (KBD) and Keshan disease (KD) were identified in a low-Se belt from the Heilongjiang Province of Northeast China to Yunnan province of Southwest China. Kashin-Beck disease (named after the two Russian scientists who first described it between 1861 and 1899) (*In*: Fordyce 2005) is an endemic osteoarthropathy (stunting of feet and hands causing deformities). The etiology of KD and KBD is still a matter of debate.

Keshan disease (name derived from an acute outbreak in Keshan County, northeast China, in 1935, and since then the incidence of the disease has declined) is an endemic cardiomyopathy (heart disease) that mainly affects children. On the other hand, *selenosis* occurs in two seleniferous regions of China, Western Hubei Province and Southern Shaanxi Province. Studies being carried out indicate that endemic *selenosis* is related to the occurrence of Permian Se-enriched carbonaceous shales with an average Se concentration estimated at 143.9 mg/kg (Mou et al. 2007), whereas the average Se content of the worldwide shale is 0.06 mg/kg (Fordyce 2005). Hair and nail loss, disorders of the nervous system, skin and poor dental health, garlic breath, and paralysis were the symptoms reported.

The range between dietary deficiency (<40 μg/day) and toxic levels (>400 μg/day) are narrow (Yang and Xia 1995; WHO 1996). In fact selenium is recognized as a dietary requirement in amounts ranging from 0.04 to 0.10 mg kg^{-1} in food (IAEA 1994). Selenium intake of 40 μg/day is needed for the maximal expression of glutathione peroxidase GPx for the protection against oxidative stress (Tapiero et al. 2003). It also contributes to the functioning of the immune system (Beck 2001) and normal growth and development (Biri et al. 2007). Selenium intake less than 40 μg/day increases the risk of oxidative stress-related diseases such as cardiovascular disorders and some cancers, and extremely low intake of <20 μg/day might result in clinical Se deficiency disorder, i.e., a congestive cardiomyopathy called Keshan disease (Fairweather-Tait et al. 2011).

According to Ngigi et al. (2020), selenium has not been considered an important public health issue in Africa. Using a case study from central Kenya highlands, the authors made a cross-sectional survey assessing the Se status of agricultural soils, foods, hair, and actual average dietary Se intake of the local population and investigating the soil-food Se concentration and Se intake-individual Se status relationships. It was found out that soil's characteristics contribute to the variation in Se concentration in foods and consequently the dietary Se intake and that a low diversified diet is a key contributing factor to inadequate dietary Se intake in the region.

The assessment of Se status is most frequently done by using plasma selenium, although plasma or erythrocyte glutathione peroxidase measurements are also widely used (Shenkin 2008). Very recently Ngigi et al. (2020) have shown that selenium determined in hair is a sensitive and reliable indicator of dietary Se intake.

Sr *Strontium* is a chemical element with characteristics similar to those of the element calcium (Ca).

It is known that strontium, which in the ionic form (Sr^{2+}) has a dimension a little higher than the Ca^{2+} ion size, enters the composition of the bone and cartilaginous tissues, being important for the stabilization of the respective structures. So much so that one of the medicines used to combat *osteoporosis* and *osteoarthritis* diseases, so common and incapacitating, contains strontium. It is the case of strontium ranelate, a salt of ranelic acid, which when taken orally at least delays the progression of osteoarthrosis and improves the associated symptomatologies. Also, strontium-alendronate in bio-metal organic frameworks (bio-MOFs) is proposed to combat osteoporosis. It is believed that Sr stimulates *osteoblasts* (the cells that create the bone tissue) and increases bone mineral density (BMD).

It is the strong presence of Sr in the carbonated or limestone biogenic sands that occur on the beaches of the island of Porto Santo of the Autonomous Region of Madeira, which justifies the positive effect of the famous and traditional sand baths. Psammotherapy or arenotherapy are the technical names attributed to therapies based on the use of sand baths that are taken locally. The carbonate-rich sands or biogenic calcareous sands of the beaches of Porto Santo are made up of three minerals that are calcium carbonates: *calcite*, *calcite-Mg* also called *magnesian calcite*, and *aragonite*. And, the Sr^{2+} ion relatively larger than the Ca^{2+} ion is particularly present in the orthorhombic and more open structure of aragonite by partially replacing the Ca^{2+} ion and not in the trigonal structure of calcite.

The Mg^{2+} ion is also relatively abundant in the carbonated biogenic sands of Porto Santo, forming part of the structure of *magnesian calcite* (Mg calcite).

Gomes and Silva (2012), in the bilingual book titled *Ilha do Porto Santo: Estancia Singular de Saúde Natural/Porto Santo Island: Unique Natural Health Resort*, show the physical and chemical properties of biogenic carbonate sand occurring on Porto Santo, properties that justify the positive therapeutic effect of traditional sand baths that were taken outdoors in the dry sand that occurs in the transition zone from the beach to the frontal dune, sand that is naturally heated by solar radiation.

Fe *Iron* is a mineral vital for cellular homeostasis. It is essential for the formation and functioning of red blood cells whose *hemoglobin* is a *metalloprotein* transporting oxygen into the bloodstream to all organs and tissues; in the form of Fe^{2+}, it is positioned at the center of the heterocyclic organic rings called *porphyrin* that makes up the hemoglobin; participates in oxidation-reduction reactions, especially in respiration; is important for brain function; and has physiological effects associated with *myoglobin*, *ferritin*, and *iron-containing enzymes*; Fe is required for myoglobin function in skeletal muscle.

Iron is present in a variety of foods, but only a small percentage of iron that is ingested is absorbed in the gut. Iron that comes from animal products (called *heme* iron) is more easily absorbed by the body than iron found in non-animal foods.

Iron status is largely maintained by the regulation of absorption in the upper small bowel. *Heme* iron is absorbed separately and more efficiently than no-hem iron, which is improved by reducing agents such as vitamin C, which also forms chelates with iron.

Mucosal cells regulate the amount of Fe absorbed, which is then carried by *transferrin* to the tissues where uptake is controlled by the expression of a membrane bound receptor for transferring. Iron is stored in the liver and bone marrow in the form of ferritin. The presence of copper, cobalt, and manganese in the human body facilitates the absorption of iron; also, vitamin C obtained through the ingestion of citrus fruits, green peppers, broccoli, strawberries, and cabbage expedites iron absorption. Calcium and caffeine both inhibit the absorption of iron.

Normal human infants are born with enough iron in their tissues to support an entire year of growth and therefore do not need iron supplements. Babies who are fed iron-fortified infant formulas can suffer from the proliferation of foreign bacteria in the gut, resulting in the production of gas, bloating, and the associated discomforts of these problems. Iron poisoning can occur if children consume adult doses of iron supplements, and toxicity has even been known to occur from cooking in cast iron pans.

The perfect synchronism of intestinal absorption, use, and storage of Fe is critical for maintaining a balance in the organism. Disorders of these processes may lead either to Fe deficiency or to Fe overload, both of which have important consequences for the patients. The signs of Fe deficiency become progressively severe, with *microcytic hypochromic anemia*, impaired physical activity and endurance in adults, and cognitive impairment in children. Excess Fe absorption causes a disease called *hemocromatose*.

Once excess iron has been absorbed by the gut, the body has no means of eliminating it. Iron toxicity due to elemental iron is so damaging to the tissues that the body produces specific proteins that surround free iron and keep it away from living cells. Between 70 and 80% of free Fe is sequestered inside the spherical molecule called *ferritin*, and the remainder is bound within the protein called *hemosiderin*. *Ferritin* and *hemosiderin* are formed in the liver, bone marrow, and spleen. When a cell needs iron, *ferritin* and *hemosiderin* attach to a transport protein called *transferrin* and are delivered to the cells via the bloodstream.

There are many laboratory tests to assess iron status; serum Fe and Fe binding capacity (*transferrin*) are widely used, but the concentrations of both of these are markedly reduced by the acute phase response. Serum ferritin is usually the best marker of iron status (Shenkin 2008).

In the USA, Fe DDR is 10 mg/day for adult men and 15 mg/day for adult women (additional 15 mg/day recommended during pregnancy).

Cr *Chromium* helps glucose metabolism and regulates blood sugar levels; chromium supports the action of insulin by helping the sugar to enter the cells, and, if the chromium in the body is insufficient, the insulin produced cannot efficiently perform its function; chromium can exist in the forms Cr^{2+}, Cr^{3+}, and Cr^{6+}, Cr^{3+} species being the most abundant in the environment essential in terms of health. Cr^{6+} is easily absorbed by the tissues being strongly toxic with effects on the liver, kidneys, and hematopoietic system. The deficiency of Cr causes changes in the glucose and lipid metabolism and is associated with diabetes and cardiovascular and nervous system diseases; Cr^{3+} in trace amounts is possibly required for sugar and lipid metabolism, although this issue remains in debate. However, the mechanisms of Cr action still are poorly understood (Di Bona et al. 2011). Chromium increases the action of insulin, possibly through amplifying insulin receptor tyrosine kinase activity. This may lead to an improvement in glucose tolerance in some individuals.

The assessment of Cr status is extremely difficult due to the very low plasma concentrations and the difficulty in obtaining noncontaminated specimens. However, plasma concentration may be available help in specialized laboratories. The best assessment may be the response of glucose and insulin to chromium supplements (Shenkin 2008).

The total Cr content in the human body is around 6 mg. The highest Cr levels in are found in the kidney, liver, intestine, thyroid gland, bones, and cartilage.

The Cr RDA is between 0.1 and 0.2 mg/day, but when the diet is associated with the use of vitamin-mineral supplement, the total should not exceed 0.7 mg/day. Dietary Cr is present both in inorganic and organic forms.

Cr is absorbed as Cr^{3+}, and in the bloodstream, it binds to transferrin and transported to the target tissues in the form of Cr transferrin and Cr chromodulin (Brock 1985).

Co *Cobalt* is a bio-essential trace element that promotes the formation of the red blood cells. Co is an essential metal constituent of vitamin B12 and is mainly cumulated in the liver, pancreas, heart, and bones. In the bloodstream, Co may be present as Co^{2+}. The average Co content in the human body is around 15 mg, and the optimal daily intake is above 0.3 mg. The liver and kidney are the organs richest in Co (Lindh 2013).

Very high contents of protein and iron in diets slow Co absorption in the gastrointestinal tract; in contrast copper and zinc enhances Co absorption. An excess of Co can lead to the disturbance of iodine metabolism in the thyroid gland.

Unlike other trace elements such as Zn, Cu, Se, and Mn, Co takes part in the functioning of a limited number of enzymes.

Ni *Nickel* is a trace element considered bio-essential, but which precise functions are still unknown. Ni DDR is between 5 and 20 μg/kg/day; higher values may be carcinogenic.

Schroeder et al. (1974) and Nielsen and Ollerich (1961) are some of the few references found in the literature.

Cu *Copper* is one of the essential trace elements in humans, and disorders associated with its deficiency and excess have been reported (Aoki 2004).

Copper promotes the formation of the red blood cells and connective tissue; acts as a catalyst to store and release iron to help the formation of hemoglobin; has an important role in redox reactions; contributes to the functioning of the central nervous system; and is one of the main cofactors of many enzymes (*cuproenzymes*). Its deficiency can adversely lower cholesterol and glucose, control blood pressure, and heart function as well as bone mineralization, while its excess can cause the uncontrolled oxidation of proteins, lipids, and other cellular components.

Deficiency of Cu is rare, but it has been observed in TPN and causes normocytic hypochromic anemia, neutropenia, and skeletal disturbances.

The clinical symptoms associated with Cu deficiency are extremely diverse: anemia, leucopenia, bone lesions, and vesical diverticula. The best markers of Cu status are plasma Cu or ceruloplasmin, although the acute phase response will cause an increase due to increased ceruloplasmin synthesis. Cu concentrations also increase during pregnancy and with the use of oral contraceptive pill (Shenkin 2008).

The Wilson's disease, named after the British neurologist Samuel Wilson, is a genetic disorder in which excess Cu builds up in body, particularly in the liver. The disease symptoms are typically related to the brain and liver. Liver-related symptoms include vomiting, weakness, fluid buildup in the abdomen, swelling of the legs, yellowish skin, and itchiness. Brain-related symptoms include tremors, muscle stiffness, trouble speaking, personality changes, anxiety, and seeing or hearing things that others do not. The disease it is caused by a mutation in the protein ATP7B gene.

The Menkes disease or Menkes syndrome is a genetic disorder of copper transport in the body, and a disorder of Cu absorption and excretion leading to Cu deficiency, that is, characterized by tortuosity and winding of arteries and increased capillary fragility, kinky hair, growth failure, and nervous system deterioration.

In the USA, Cu DDR is 0.9 mg/day for adult men and women.

Mo *Molybdenum* contributes to normal growth and development and is the activator of three important enzymes: aldehyde dehydrogenase, sulfite oxidase sulfite, and xanthine oxidase.

Mo deficiency is generally a genetic disorder, and it can inhibit growth and development, especially in the prenatal and neonatal stages, nausea, and disorientation; Mo excess may cause abnormal development of high levels of uric acid.

It is supposed that molybdenum enters the human organism in the form of MoO_4^{2-}. Mo deficiency is observed in persons maintained at parenteral nutrition for a long period of time.

The recommended level of Mo intake is 75–250 μg/day, and the minimal daily requirement is 25 μg/day, and most of it is absorbed in the gastrointestinal tract.

Green vegetables and beans are the food richer in Mo. The main Mo-containing organs are the liver and kidneys. Mo deficiency can be corrected by Mo supplements.

Zn *Zinc* is an essential component of more than 200 enzymes involved in digestion, metabolism, reproduction, and wound healing; also plays an important role in the immune system making it more resistant to infections; and is essential for biological functions such as growth, appetite, testicular maturation, skin integrity, and mental activity. Its deficiency can cause skin lesions, growth retardation, anemia, and immune deficiency. Increased levels may cause complications in the gastrointestinal tract manifested by burning and pain in the mouth and throat and vomiting, related to *pharyngitis* and *esophagitis*; it is important component of the DNA acting as stabilizer of the phosphate groups and coordinator of the organic bases.

Zinc is absorbed after the digestion of macronutrients in the gut, but the absorption may be markedly affected by ingestion of large amounts of other elements such as iron or copper, or by large amount of fiber food, which reduce Zn bioavailability. Zn is mainly transported in the plasma bound to albumin.

Zinc severe deficiency can cause alopecia, diarrhea, delayed sexual maturation, eczematous skin rash, and impaired appetite. The most widely used marker of Zn status is plasma Zn concentration which correlates reasonably well with intake, provided there is no inflammatory response (Shenkin 2008).

In the USA, Zn DDR is 15 mg/day for adult men and 12 mg/day for adult women (an additional 3 mg/day during pregnancy and 7 mg/day during lactation). Yanagisawa (2004) provides interesting information on zinc deficiency and clinical practice.

F Fluorine as *fluoride* has a well-established beneficial action in the human beings. Fluoride participates in the structure of the basic constituent *hydroxyl-fluorapatite* of the bones and teeth; [F] <0.5 mgL^{-1} favors the development of dental caries; >0.5 [F] <1.5 mgL^{-1} has no adverse effects; [F] > 1.5 mgL^{-1} favors the development of *dental fluorosis* and *skeletal fluorosis*.

The mechanisms through which F has beneficial effects are making hydroxyapatite of the teeth enamel and dentin less soluble and thus more resistant to acid attack and altering calcium, magnesium, and/or phosphorus metabolism and tissue deposition and/or use (Whitford 2006; Ophaug and Singer 1976).

Mn *Manganese* is a component of enzymes involved in oxidation reactions and has an important role as antioxidant and activator of enzymatic systems; its deficiency can affect the bones, brain, and reproductive system. Increased levels may induce neurological disorders such as decreased concentration and memory, fatigue, headache, dizziness, imbalance, insomnia, tremor, sweating, and libido. Absorbed Mn accumulates mostly in the liver, pancreas, kidneys, and bones. Mn and Fe compete to form complexes with transferrin.

Mn metalloenzymes are involved in amino acid, cholesterol, and carbohydrate metabolism. Glycosyl and xylosyl transferases are important in proteoglycan synthesis, which is required for bone formation (Shenkin 2008). Mn-activated enzymes help in the metabolism of cholesterol amino acids and carbohydrates.

As a bio-essential element, the total content of Mn in the human body is 10–20 mg, the daily requirement is 3–5 mg, and the minimal requirement is 0.74 mg/day or 10.8 μg/kg weight (Lindh 2013).

Manganese is absorbed as Mn^{2+} and Mn^{3+} in the gastrointestinal tract and as Mn^{3+} `which` occurs in transferrin. Dietary manganese is poorly absorbed (less than 5%). It is transported in the blood bound to transferrin and albumin (Shenkin 2008).

V *Vanadium* is considered by many researchers also an essential trait or vestigial element that in the biological materials occurs in the anionic species vanadate

(VO_3^{1-}) and vanadyl VO^{2+}, the first predominant in the extracellular fluids and the second in the intracellular fluids. In the USA, V DDR ranges from 6.2 to 18.3 μg/day.

Goc (2006) published a review that enhances the biological insulin-mimetic activity of vanadium compounds manifested in their action to normalize the changes observed in both clinical and experimental diabetes through the regulation of carbohydrate and lipid metabolism and the removal of secondary symptoms of the disease.

Other elements or minerals such as B (boron), Br (bromine), Be (beryllium), Li (lithium), Ba (barium), Al (aluminum), U (uranium), Ti (titanium), Sn (tin), and Rn (radon) may have positive or negative effects, confirmed or awaiting confirmation, in human health.

Regarding *lithium* (Li), for instance, studies have been conducted in, for example, Denmark, on the links between lithium in drinking water and suicide rates. Some epidemiological studies suggest that the addition of low levels of lithium in drinking water results in lower suicide rates (Takeshi et al. 2009). One important link between lithium and mental health is the long-established use of lithium salts as stabilizers for mental disorders. Lithium has also been used to increase the efficacy of other antidepressants.

4.5 Mineral Supplements

The so-called mineral supplements or nutritional supplements, as a rule, consist of the association of certain minerals and vitamins, which are classified micronutrients. Micronutrients are required for nearly all metabolic and development bodily processes. Micronutrients are responsible for ensuring that everything in the body works well and efficiently. In turn, macronutrients comprising proteins, carbohydrates, and lipids are the only sources of energy for humans.

Supplementation of the diet with micronutrients is a common practice because of the growing concern about health, growing commercial availability, and strong advertising appeal, but indiscriminate consumption can pose health risks.

Should we take supplements? Should we not? If so, what kind of vitamins and minerals? Vitamins are organic compounds normally present in minimal quantities in foods and which may not be synthesized by the body in amounts adequate to suppress normal physiological needs.

There are two major groups of vitamins: vitamins that need fat to be absorbed and which are therefore called liposoluble (A, D, E, and K) and water-soluble vitamins, such as those in complex B, which if they are not stored in appreciable quantities, their regular consumption is a necessity.

Minerals that are essential substances in the hard tissues of the body, such as the bones or teeth, are also divided into two groups: macroelements (e.g., calcium, magnesium, sodium, and potassium) and microelements (e.g., copper, iodine, zinc, and fluorine).

Quantitatively calcium is one of the most represented minerals in the human body. About 99% of calcium is stored in the bones and teeth. Adults need 1000 mg Ca/day, which increases with age (women over 50 and men over 70 need 1200 mg Ca/day). In mineral supplements Ca can occur in various chemical forms, the two main forms being calcium carbonate and calcium citrate, the latter more easily absorbed and bio-available than the former.

The Food and Nutrition Board of the US Institute of Medicine has defined the Recommended Dietary Allowance (RDA) values for 29 vitamins and minerals (*In:* Ward 2014). For minerals the following values are noted: K, 4.7 g/day; Na, 1.2–1.5 g/day; Cl, 1.8–2.3 g/day; Ca, 1000–1200 mg/day; Fe, 8–18 mg/day; Mg, 310–420 mg/day; P, 700 mg/day; Zinc, 8–11 mg/day; F, 3–4 mg/day; Mn, 1.8–2.3 mg/day; Cu, 900 μg/day; Cr, 20–35 μg/day; Se, 55 μg/day; Mo, 45 μg/day; and I, 150 μg/day.

For vitamins the following values are highlighted: vitamin A, 700–900 μg/day; vitamin C, 75–90 mg/day; vitamin E, 15 mg/day; vitamin B12, 2.4 μg/day; and vitamin D, 15–20 μg/day.

Specialists in nutrition and dietetic recommend a balanced and varied diet to obtain the essential macronutrients and micronutrients. People who do not consume adequate amounts of certain foods may have nutrient shortfalls. In addition, there are times throughout the life cycle when the body requires more nutrients than the typical diet may provide, such as iron (Fe) during pregnancy and vitamin B_{12} after the age of 50 years (Dietary Guidelines for Americans, 2010). Also, in the USA, as defined by the Dietary Supplement Health and Education Act of 1994, dietary supplements are intended to supplement the diet and not to prevent disease.

Ignoring the needs of vitamins, disesteeming their presence, absence or insufficiency in the body, is a mistake. On the other hand, overeating them can also be problematic. In all three situations, the consequence may be a “specific deficiency”: “Hypovitaminosis is harmful to health, but hypervitaminosis is also harmful.”

The efficacy of vitamin and mineral absorption is different when “Integrated or not in the nutritional matrix of a food.” A varied, balanced, and complete diet is one that seeks to “Optimize the intake of vitamins and minerals through food,” namely, vegetables, fruits, vegetables, and cereals. For this reason, taking supplements regularly without discretion may seem like a problem. According to nutritionists, “Before you start taking a multivitamin it is important to evaluate your vitamin levels and consult a nutritionist.”

4.5.1 Essential Functions of Mineral Supplements and Vitamins

According to the Portuguese Association of Nutritionists vitamins and minerals are micronutrients, that is, nutrients that, although they do not provide energy, have specific functions essential to the proper functioning of the body. While vitamins act as regulators of proteins, carbohydrates and lipid metabolism, minerals acting along with enzymes are key-factors for energy metabolism.

4.5.2 Risks of Minerals and Vitamins in Excess

As is the case for macronutrients, also for micronutrients, there is a daily dose recommended (DDR). The DDR is the reference values below which the body is in nutritional deficiency. However, overcrowding them is also dangerous since the vitamins and/or minerals in excess can be toxic.

Consumption of vitamin and mineral supplements at doses exceeding RDA by well-nourished people can have adverse effects. For example, prolonged intake of high doses of ascorbic acid (vitamin C) may result in kidney stones, decreased coagulation time, and gastrointestinal problems, among other physiological disorders; and excess zinc induces a secondary deficiency of copper and decreases the concentration of "good" cholesterol (HDL).

Although it is recognized that the practice of physical activity can increase the need for some vitamins and minerals, most people can obtain the necessary dose through a varied and balanced diet – which, in the Portuguese case, corresponds to respecting the indications of the "wheel of food." Thus, only those who take a low-energy diet on a long-term basis are at risk of developing a nutritional deficiency of vitamins and/or minerals and may benefit from taking a supplement. But even if there is an obvious nutritional deficiency, there is no scientific evidence to support the widespread use of supplements to improve athletic performance. In healthy people, the use of vitamin and mineral supplements should be looked at judiciously, if at all.

Professional athletes, due to their interest in maximizing their physical performance, may seek to use supplements but should always consult with a specialist in sports medicine beforehand.

4.5.3 Is It Needed to Take Mineral Supplements?

New products based on vitamins and minerals are often released on the market, with an increase in the supply of vitamin and/or mineral supplements in the market. For some time, the importance of vitamins was attributed only to the nutritional and disease prevention functions resulting from their deficiency.

Recently, several research works have focused on the role that these micronutrients play in maintaining health, specifically in reducing the risk of developing chronic diseases such as coronary diseases, cancer, and diabetes.

In healthy people, the use of vitamin and mineral supplements should be looked at judiciously, if at all. Professional athletes, due to their interest in maximizing their physical performance, may seek to use supplements but should always consult with a specialist in sports medicine beforehand.

Guallar et al. (2013), in an article entitled "Enough is enough: Stop wasting money on vitamin and mineral supplements," say that there is sufficient evidence, particularly in the USA, where the use of multivitamin supplements among adults increased from 30% between 1988 and 1994 to 39.5% between 2003 and 2006, to advise against routine supplementation, message that is especially true for the general population with no clear evidence of micronutrient deficiencies, representing most supplement users in the USA. The authors believe that supplementing the diet of well-nourished adults with (most) minerals or vitamins supplements has no clear benefit and might even be harmful.

In some countries the regulation or legislation on the consumption and safety of the use of vitamin and mineral supplements is very important. For example, *Abe-Matsumoto* et al. (2015) present studies related to this matter in Brazil. Many of the investigations focus on foods containing vitamins C and E, as well as beta-carotene, a precursor of vitamin A, which are known to have antioxidant activity and play an important role in protecting the body against free radicals (Boni et al. 2010; and Ryan et al. 2010).

Today, it is common to see in the market a category of vitamin supplements with commercial appeal to antioxidants. Like the antioxidant vitamins, vitamin D has also been the subject of much research in the last 20 years due to its apparent generalized deficit in humans. Really vitamin D is not a vitamin.

In 1931, the German chemist Adolf Windaus from the University of Gottingen found out the same structure of the *steroids* hormones, such as cortisol and sexual hormones.

Being discovered in 1990s the receptor of vitamin D, it was assumed the specificity of this hormone, since unlike other hormones a specific target organ had not been identified. Vitamin D appears to be a biochemical key of decisive action for various fundamental life processes. Hence, without vitamin D, life would be impossible.

In 2020, due to *COVID-19*, the major pandemic suffered by the industrialized man, renewed scientific and medical discussion is taking place about the effective functions of vitamin D (Marinho 2020). Cholecalciferol, also known as vitamin D_3, is a type of vitamin D which is synthesized by the skin when exposed to sunlight and can be used in dietary supplements to treat and prevent vitamin D deficiency.

Throughout the decades, vitamin D was assumed as a key element in the control of bone metabolism. Presently, the importance of vitamin D goes beyond this function. Either present in food, or photosynthesized through the skin, vitamin D works in the human body in a very active form. Now, we know that vitamin D has relevant functions with anti-inflammatory, antioxidant, and antimicrobial effects, mainly in diseases such as hypertension, diabetes, and cancer. Also, there is scientific evidence about the protector effect of vitamin D in viral respiratory disorders.

There are published studies about vitamin D levels in different regions of the world. For instance, in the southern countries of Europe, such as Spain, Italy, Greece, and Portugal, the percentage of people with vitamin D deficiency is higher than in the northern countries where sunlight has lower incidence. However, in the northern countries, the less sunlight incidence is compensated by vitamin D supplementation, which traditionally is not practiced in southern countries. In the southern countries, such as Spain and Italy, the *COVID-19* pandemic has revealed great severity, whereas in the northern countries, such as Finland and Denmark, the pandemic is less severe.

Taking into account the ratio of the *number of severe patients/otal number of patients in a million of people*, it is significantly lower in the northern countries relative to the southern countries: 0.07 in Denmark and 0.13 in Finland versus 1.1 in Italy and 1.9 in Spain. In what concerns vitamin D levels, the prevalence of individuals with severe deficiency ranges between 0.4% and 8.4% in the northern countries versus 4.6%–30.7% in the southern countries.

Recently the researchers of the University of Turim, Italy, found out a severe deficiency in vitamin D in *COVID-19* patients bearing obesity, diabetes, and hypertension disorders. Vitamin D also enhances cellular immunity, in part by reducing the cytokine storm induced by the innate immune system. Vitamin D can reduce risk of respiratory tract infections through mechanisms that include induced cathelicidins and defensins able to lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Such generates both pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infection, as has been observed in *COVID-19* patients (Grant et al. 2020). Also, it has been shown that these risky patients take medicines containing estatinas or glucocorticoids and not any supplementation.

Magnesium (Mg) is a cofactor in more than 300 biochemical reactions throughout the body, influencing protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation; it is assumed that Mg is a mineral essential to maintain a healthy immune system (Gaby 2011; Lipski 2012; and Gröber et al. 2015).

Therefore, could Mg-rich supplementation help in *COVID-19* pandemic prevention? A diet rich in eggs, meat, fish fat, and milk are also rich in Mg.

Weiss et al. (2018) mention that a suboptimal magnesium status is likely widespread in the USA, and the increasing evidence links this deficiency to many chronic diseases. The authors evaluated Mg absorption, cellular serum uptake, and clinical effectiveness and toleration (experience shows that high supplementation often leads to bowel intolerance) of a timed-release formulation containing dimagnesium malate supplement with vitamins B6, B12, and folate (MagSRTTM) applied in a standard clinical population, and found out that the Mg from the supplement was well absorbed and tolerated. Zinc (Zn) is another mineral reckoned to boost the immune system.

In recent years, vitamin D deficiency has increased due to modern lifestyle habits and mainly because of the limited exposure to the sun by the population in order to avoid skin cancer (Unger et al. 2010).

Vitamin C is another powerful antioxidant recommended to treat infection of the upper respiratory tract; hence it is recommended to be used in the nutritional treatment of coronavirus infection.

The use of calcium supplements for the prevention and treatment of *osteoporosis* has been advocated for several decades; however, recent studies have shown that such use may increase the risk of cardiovascular events, kidney stone formation, and gastrointestinal problems (Bolland et al. 2015; Taksande and Woecester 2014).

Calcium with vitamin D is one of the most common combinations of nutrients in supplements, since vitamin D acts as a key hormone for calcium homeostasis and for the healthy development of the bone system. *Denosumab* has been shown to be effective in the treatment of osteoporosis and prevention of osteoporotic fractures (Papapoulos et al. 2015; Scott 2014).

4.5.4 The Risks of Mineral Supplements and Vitamins on Human Health

The quantity of micronutrients required for each individual depends on several factors, such as sex, age, level of physical activity, and the presence of pathologies, among others. In general, there is no need to make nutritional supplementation.

As the definition of supplement says, vitamin and/or mineral supplements are only indicated for people who need to supplement the diet if it is deficient, since the lack of nutrients can lead to the development of diseases.

The lack of vitamin A, for example, leads to the development of night blindness; the lack of vitamin C is responsible for scurvy; iron deficiency causes anemia.

Currently, vitamin D deficiency, commonly known as “sunshine vitamin,” is considered an epidemic, and supplementation of this vitamin has been increasingly recommended. As the sun is the natural source richest in vitamin D that is synthesized in the skin, it is surprising that so many people in Portugal, one of the sunniest countries in Europe, are deficient in this vitamin.

In the USA, the reference value for vitamin D is 15 μg/day, but scientists from the University of California, in San Diego, recommend values 11–12 times higher. The same happens in the UK where the reference value is 10 μg/day, but scientists recommend values are 17 times higher.

People with dark skin absorb less UV light and so synthesize less vitamin D than people with white skin. Vitamin D also can be obtained through the ingestion of some types of food, particularly fish fat. Vitamin D is particularly important to maintain a normal immunological function and to keep the bones healthy.

A study conducted by the “Centro Hospitalar da Universidade de Coimbra” shows that about 65% of the Portuguese population has low vitamin D levels in the body, and it is worrying that the problem affects both the older and younger generations. Compared with people from northern European countries, the Portuguese people had lower vitamin D levels.

Another study conducted between 2011 and 2013, in a group of 3092 individuals, at the "Faculdade de Medicina da Universidade de Coimbra" in collaboration with the Nova Medical School of the Universidade Nova de Lisboa, more than 20% of the Portuguese adult population has vitamin D levels well below the normal levels corresponding to the risk situations, and only 3.6% of the adult population has normal or higher vitamin D levels.

Scientists agree that the optimum vitamin D level in the blood should be around 50 nmol/L and consider that vitamin D levels less than 20 nmol/L mean severe deficiency.

Many people spend much of the day indoors not catching enough sunshine, and in cases where they do sun exposure, they usually use sunscreen that blocks vitamin D synthesis in the skin.

Vitamin D was said to have benefits only for bone health, but recent studies have demonstrated broader benefits to the immune system, mental health, and muscle function. However, some cases of intoxication due to excess vitamin D (about 1000 times the recommended dose), especially in children, have resulted in *hyperkalemia*, *nausea*, *polyuria*, and *fatigue* (Araki et al. 2011).

Kara et al. (2014) observed seven cases of vitamin D intoxication in children as a result of manufacturing error of a fish oil supplement. The product showed an excessively high dose of vitamin D, causing *hyperkalemia*, loss of appetite, vomiting, weight loss, and constipation after ingestion of 4000 times the indicated dose.

Ingesting mineral supplements can be harmful. People, in an attempt to enjoy good health, end up causing the most confusion in the body.

4.5.5 Is It Possible to Investigate the Mechanism of Mineral Absorption in the Human Body?

What is the mechanism that regulates the absorption of minerals? For the time being, it is unknown how the absorption itself occurs, that is, what kind of reaction happens in the wall of the intestine that causes a mineral to pass into the bloodstream.

What is known is that most of the minerals are only partly absorbed. Minerals with 100% utilization can be considered exception, for example, sodium, potassium, iodine, and chlorine.

Using radioisotopes of the minerals calcium, zinc, selenium and iron, these minerals can be followed in the body by a device called a high-resolution gamma-ray spectrometer. By the radiation captured, this equipment measures the amount absorbed of a certain mineral and also shows precisely the regions of the body on which it concentrates. These experiments have proved, once and for all, that by ingesting larger quantities of minerals, one is taking advantage of less minerals. More than that, these new studies make it clear that reduction in absorption should be a defense mechanism of the body itself. For when the dosage of a single mineral is increased, it breaks a delicate balance between all the minerals, that is, the abnormal majority concentration of one mineral in the organism harms the other minerals.

4.5.6 Will There Be Any Interference and Competition Between Minerals?

There is indeed a real competition between minerals. For example, *zinc*, *copper*, and *iron* are very similar substances from the chemical point of view. Therefore, it is natural that they compete for the same area of absorption in the intestine.

In an experiment with rats when the concentration of *zinc*, a metal involved in the production of the hormone *insulin*, was increased in the diet, a decrease in the *hemoglobin* content for which *iron* production is indispensable was noted. In the organism that ingested more *zinc* than normal, less *iron* was available for the production of *hemoglobin*. The same happened when the proportion of copper in the diet was increased. Also, when the dosage of zinc and iron in the diet was increased, these two minerals took the place of the copper stored in the mouse's liver.

4.5.7 Deceiving Publicity of Mineral and Vitamin Supplements

In Portugal, the Infarmed, the Order of Pharmacists or Chemists, and the Medical Order classify as misleading advertise the insistent publicity in the Portuguese mass media, television in particular, for calcium and vitamin D supplements such as "calcitrin" and "calcium plus" as being effective in preventing bone fractures in the elderly, when clinical trials do not indicate appreciable evidence of fractures between groups of individuals taking and not taking these supplements.

Fiolhais and Marçal (2017) present interesting information on this issue – *misleading advertising*.

According to Grey and Bolland (2015), available medical evidence indicates that calcium and vitamin D supplements do not reduce the risk of fractures by more than 10% at the expense of much more significant detrimental effects, including cardiovascular and renal diseases.

For Bolland et al. (2010), randomized studies suggest that calcium supplements without coadministered vitamin D are associated with an increased incidence of myocardial infarction; the calcium supplements produce vascular effects.

None of the supplements being marketed are subject to the requirements of efficacy and safety, the control that medications are seriously subject, it may reconstitute bones already weakened by osteoporosis as the viewer is led to believe.

4.6 Toxicity Due to Excess or Deficiency of Minerals in the Elemental Form

The human body produces daily the essential nutrients necessary for life. Effectively, the human body is similar to a tissue-producing factory, such as the skin, muscle, and bone, and feeding the red blood cells or erythrocytes that carry nutrients and oxygen to all parts of the body. To fulfill these functions, the human body needs raw materials, minerals and vitamins (micronutrients that are organic compounds or fat soluble, as are the cases of vitamins A, D, E, and K, or water soluble, as with vitamins B and C), both obtained through food or the so-called food supplements.

The deficit or excess of vitamins and minerals can be bad for health. For example, there is scientific information indicating that vitamin A and vitamin D become toxic when ingested in doses greater than ten times the recommended daily allowance (RDA).

On the other hand, vitamins and minerals can interact with each other. For example, vitamin D makes the body able to extract Ca from food at the level of the intestine instead of extracting it from the bones. Vitamin C also helps in the absorption of Fe but prevents the assimilation of Cu, another essential micronutrient. Not only do the chemical properties of minerals have positive effects or are convenient for human health. In fact, some physical properties of the minerals are also important, particularly the thermal properties, for example, heat capacity and heat diffusivity, when clays or special muds and pre-heated special sands are used in topical applications (Gomes and Silva 2001).

Other physical properties such as color, hardness, abrasiveness, particle size and shape, purity, adsorbent power, absorbency, plasticity, and rheology may be equally useful, either when the minerals participate as active ingredients or when they participate as excipients in pharmaceutical formulations, or even when they participate in the composition of cosmetics.

Nieboer and Sanford (1984) provide examples of the pharmacological use of *minerals* and *metals*, such as:

1. Al hydroxide and Ca and Mg carbonates in antacid formulations
2. Zn oxide in ointment formulations with healing effects and others
3. Ag, Hg, and Zn in antiseptic and germicidal formulations

In radiology, certain minerals are very important, such as *barite* (barium sulfate that is incorporated into emulsions that are taken orally before radiological examinations of the digestive system), *silver* (which participates in the composition of photographic films used in radiology), and *lead* (which is incorporated into the protective clothing of radiology technicians).

As macro- or micronutrients, the aforementioned essential elements may be good, toxic, or lethal, depending on the individual dosage. This principle was established long ago. Indeed, according to Paracelsus (1493–1541 A.C.), “All substances are poisons; there is none other than poison; the correct dose differentiates the poison from the remedy.” Paracelsus considered that any increase in the amount or concentration of the elements causes negative biological effects which may lead to the inhibition of certain biological functions and eventually to death.

In many aspects of life, either too much or too little can be equally harmful. Effectively, nonessential chemicals may be tolerable, toxic, or lethal, depending only on dosage.

Figure 4.4 shows the graph of the "dose/functional response" curve indicating the optimal amount of an element required for maintaining good health as well as the amounts contributing to levels of deficiency or toxicity. The dose/response or effect curve for a specific element may differ from organism to organism, but the underlying principle of deficiency, ideal concentration, and toxicity remains constant (cited *In*: Bowman et al. 2003).

On toxicity the excess or deficiency of a certain chemical element affects the health of man and other animals and, of course, also of plants.

The elemental deficiency, either due to deficient diet or deficient metabolism, can be compensated by the so-called nutritional supplements rich in vitamins and minerals, namely, mineral salts or macronutrients, such as P, Ca, Mg, S, Na, and K, and trace minerals or micronutrients, such as Fe, Cu, Cr, Se, I, Mn, Mo, Zn, and Si. Other chemical elements that are essential for the human body are also important formers of minerals, such as O, H, C, and N.

According to Hippocrates (460–377 B.C.), "We are what we eat; let your food be your medicine and your medicine your food." Effectively, the best diet is one that is functional for the whole organism and not just for a part of it. Hippocrates believed that animal health and "place," meaning the environment where the animal lives, particularly the geological factors, are closely related, giving examples of this in his book *On Aires, Waters and Places*. Hippocrates stressed, for example, the great importance of water quality in human health.

There are chemical elements that may be toxic to humans and include heavy metals such as *lead* (Pb), *mercury* (Hg), and *cadmium* (Cd), as well as *arsenic* (As), *antimony* (Sb), and *selenium* (Se). There are chemical elements, as is the case of fluorine (F) which, not being classified as metals or as metalloids, are highly toxic. As regards metals, they are not metabolizable and are therefore bioaccumulable in the body.

Ingestion, *inhalation*, and *dermal absorption* are the routes for the incorporation of the toxic elements. And the renal route and defecation are the main routes of elimination of the metals by the organism. Fortunately, the most toxic elements are little abundant in the natural environment occurring in it as trace elements.

Rapid diagnosis of elemental toxicity is done and evaluated on blood and urine samples of the intoxicated individual comparing the values obtained with established reference values in healthy subjects.

The toxicity and therapeutic virtues of certain metals and metalloids were recognized by the Greeks, Romans, Arabs and Chinese. According to Liu et al, minerals have been used in traditional medicines since ancient times and are still used today. For example, in traditional Indian medicine Ayurveda, 8% of the recipes contain 15 kinds of minerals (metals) altogether (Joshi et al. 2017); in traditional Chinese medicines, minerals are used to assist the presumed therapeutic effects; and in

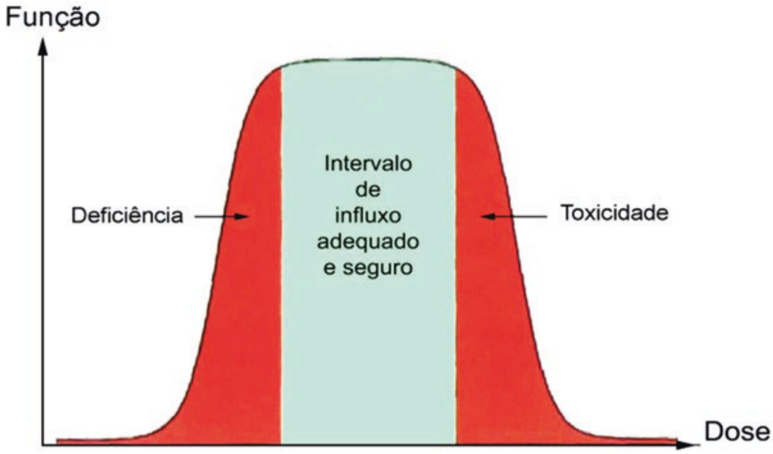


Fig. 4.4 Relationship between dose and function in the health of a particular mineral/chemical element. (Source: Lindh 2005)

Pharmacopeia of China (edition 2015, volume 1), at least 10 minerals are listed in the 1493 traditional recipes, approximately 7% of the recipes contain cinnabar (HgS) and/or realgar (As_4S_4); in traditional Tamil system of Siddha medicine, nearly half of the preparations used for diabetes treatments contain inorganics, including cinnabar and realgar; and in traditional medicines used in Sri Lanka, minerals including cinnabar and realgar can be found (Kankanamalage et al. 2014).

Among the minerals used in traditional remedies, *cinnabar* and *realgar* have received great public concern, in terms of their health safety (Liu et al. 2008a, b; Wang et al. 2015).

According to Liu et al, only sulfide forms of mercury and arsenic are used in oral traditional medicines discussed above; sulfide mercury form is used for the treatment of chronic ailments, pneumonia, nervous disorders, high fever, stroke, and syphilis (Kamath et al. 2012; Chen et al. 2012, Kan 2013; Huang et al. 2013); and sulfide arsenic form is used in the treatment of various diseases, including mouth and tongue ulcers, headache, and vertigo, and has a promising anticancer action. The chemical forms of cinnabar and realgar are major determinants of their disposition, efficacy, and toxicity.

Already in antiquity, the adverse effects of minerals and rocks on human health were pointed out and referred to. Also, several pathologies were attributed to minerals, some of them related to the processing of minerals, through metallurgical works.

Galen (129–199 A.C.), a Greek physician who became famous in Rome, produced several books and reaffirmed the potential danger of mining activities when he observed the acid fumes associated with copper (Cu) production (cited in Lindberg 1992).

Health problems attributed to metal toxicity, for example, lead and cadmium (Cd) poisoning, have occurred since ancient times in many parts of the world where mining was processed (smelting and refining of ores and ore concentrates) for the production of metals.

The poisonings due to lead, mercury, and arsenic, termed saturnism or plumbism, mercurose or hydrargyrism, and arsenicosis, occurred frequently among the Romans (Nriagu 1983, 1996, 1998). On the other hand, Hong et al. (1994) speculate about the contribution of these types of poisoning, particularly that caused by lead to the "Fall of the Roman Empire." It is known to have been a common practice for the Romans to store wine in a pot of lead.

In the civilization period called the Renaissance the first Pharmacopeia texts had classified certain medicines as well as minerals participating in medicinal applications and had regulated too the production and medicinal application of the same, situation that has coincided with the first systematics of the minerals.

At present, systematically renewed editions of Pharmacopeia from countries such as the USA, the European Union (the fifth edition is the most recent), and Britain are interesting texts worthy of being consulted.

Effectively, the best diet is one that is functional for the whole organism and not just for a part of it. In addition to the chemical elements, macro- and micronutrients, of inorganic origin, so called "minerals" or "minerals latu sensu (l.s)" and which are essential to life, foods, particularly the so-called functional foods, contain chemical components of organic origin that are equally essential for good health, such as vitamins, folic acid in cereals, and fatty acids unsaturated omega-3 existing in fish. The nature and the correct dosage of these chemicals, inorganic or organic, in foods can prevent or ameliorate disease states and improve physiological performance.

Additional historical information on the use of different minerals for medicinal purposes is conveyed by several authors, such as Bech, 1987; Robertson, 1996; Veniale, 1997; and Carretero, 2002.

Several diseases have been attributed to the influx, inhalation, and intake of polluted air and water, respectively. Minerals and certain industrial products derived from airborne minerals in the form of dust, particularly those that can be classified as nanominerals (clay minerals and nonclay minerals with particle size measured in nanometers, being 1 nm = 10^{-9}m), may cause serious problems in the respiratory system.

According to Wagner et al. (1998), the great majority of clay-based dusts are innocuous and, therefore, they only produce adverse effects in case of intense and lasting exposure. Among clay minerals, only those with crystalline fibrous habits, such as *sepiolite* and *palygorskite*, are capable of causing lung tissue damage.

The World Health Organization (WHO) draws the attention of the Government Environmental Agencies to the need to carry out research aimed at assessing the real effects of mineral dust and also of aerosols and fumes in certain diseases and pathologies. Also, due to the interaction of water with certain types of rock and soil, water may contain high concentrations of metals (among them, heavy metals, e.g., copper, zinc, lead, chromium, cadmium, and mercury, responsible for *plumbism* or *saturnism*, i.e., lead poisoning and *hydrargirose* in the case of mercury poisoning) and metalloids (e.g., arsenic and fluorine, which are responsible for diseases, *arsenicosis* in the case of arsenic and *fluorosis* in the case of fluorine), which can be very harmful to human health.

Humans are part of the natural environment, and, consequently, any human's aggressive behavior toward the natural environment will affect himself, his quality of life, and even his health.

4.7 Sources and Pathologies Caused by Potentially Toxic Minerals in the Elemental Form

The production and use of chemicals continue to grow worldwide, particularly in developing countries. This is likely to result in greater negative effect on health if sound chemicals management is not ensured. Multisectoral action is urgently needed to protect human health from the harmful effects of improperly managed chemicals.

The WHO (2010a) presents a summary of scientific evidence and provide risk management recommendations for ten chemicals or groups of chemicals of major public health concern, six of them being minerals, such as Pb, Hg, F, Cd, As, and asbestos. Within the remaining four chemicals or groups of chemicals, benzene, dioxin-like chemicals, air pollutants, and highly hazardous pesticides can provide quite harmful effects. It becomes clear that this WHO report has adopted the concept of *mineral l.s.* defined in the Preface of the present book, which encompasses minerals in both *elemental form* and *compound form* or *mineral s.s*.

Regarding toxic minerals and their hazardous effects on human health, relevant information just limited to minerals in the *elemental form* is disclosed as follows:

4.7.1 Lead (Pb)

Lead (Pb) is naturally found in minerals *galena* (PbS), *cerussite* ($PbCO_3$), and *anglesite* ($PbSO_4$). There are other sources of Pb that are anthropogenic, related to the exploration and metallurgical processing of certain ores, used as fossil fuels in transportation vehicles, in certain types of paints, and also in phosphate fertilizers.

Pb is a very poorly mobile metal in oxidizing medium. Occupational health problems related to mineral dusts and lead poisoning (Pb) were recognized in China during the Ming Dynasty (14–17 A.D. centuries, more precisely from 1368 to 1644) due to both rock fragmentation essential for the preparation of earthenware and porcelain and the use of lead in the production of glassware. In Ancient Rome, there were lethal intoxications, which only recently came to be known to have been caused by lead (*plumbum* in Latin) existing in household water circulating in lead pipes, in wine served in goblets made of tin and lead alloy, and on glassware.

George Agricola (1494–1555) reports and describes the symptoms of Schneeberger's disease (lung cancer) among miners working at the Erzgebirge silver mine in Germany, where silver minerals occur associated with uranium minerals, a disease now attributed to the inhalation of dust and radon.

Lead is a very toxic element that can attack the central nervous system. Poisoning with Pb called plumbism or saturnism can lead to anemia and liver and kidney dysfunctions. *Plumbism* or *saturnism* or yet *lead poisoning*, as a rule, is an occupational disease among typographers, painters, welders, and miners due to the inhalation of lead-containing gases and dust, lead poisoning (Pb) being manifested by the reduction of hemoglobin in the blood and consequent anemia, changes in the nervous system, and renal and hepatic impairment. The name *saturnism* is derived from the Latin word *saturnismus*, *saturne* being the name given by the alchemists to lead.

Lead distribution in the human body initially depends on the blood flow into various tissues, and almost 95% of Pb is deposited in the form of insoluble phosphate in the skeletal bones (Papanikolaou et al. 2005).

Lead poisoning can be either acute or chronic. Acute exposure mainly occurs in the place of work and in some manufacturing industries which make use of lead and can cause loss of appetite, headache, abdominal pain, renal dysfunction, and hallucinations. Chronic exposure can result in mental retardation, brain damage, kidney damage, birth defects, autism, hyperactivity, and dyslexia and may even cause death (Martin and Griswold 2009). The main sources of Pb exposure are lead-based paints, gasoline, and industrial emissions (Gerhardsson et al. 2002). Epidemiologically most common sources of lead in the home are lead-based paint, drinking water, and pottery.

The World Health Organization (WHO) in a 2013 report recommends the disposal of lead in indoor paints inside buildings. According to the Environmental Protection Agency (EPA), lead is considered a carcinogen.

Lead, in the form of oxides and sulfates, participates in the formulation of various types of paints. Lead poisoning is a clinical condition which is either due to ingestion of lead metal compounds (e.g., in drinking water) or by the inhalation of lead oxide fumes. The pipes that carry the water may be made of lead and of its compounds, which can contaminate the water (Brochin et al. 2008).

Ingestion of lead compounds is often seen in children, whereas in adults it is often due to lead inhalation. In children lead toxicity can be due to pica (e.g., dirt soil eating), the inhalation of toxic fumes, or lead-based paints.

4.7.2 Mercury (Hg)

Mercury is known by Dioscorides and Galen as *hydragyrus* and identified for its corrosive properties, being used during the Roman Empire to relieve the pain arising in the development of the dentition in the children and to aid in the gold and silver mining recovery. Mercury is known too by the nickname "quicksilver" (Swiderski 2008). This author details the role of mercury in several medical, industrial, and cultural applications. In the fields of dentistry and vaccination, mercury continues to be used as a preservative and amalgamative agent. Though modern scientists recognize mercury as a harmful environmental pollutant and one of the world's most dangerous metals, mercury was once considered a wondrous substance capable of eradicating internal disease. In the sixteenth and seventeenth centuries, mercury was used in the treatment of syphilis, though with few benefits and devastating side effects. A mercury compound was used in the 1960s as a diuretic but was quickly discontinued because of its acute toxicity.

Mercurose or *hydrargyrism* (also referred to as *acrodynia* or *pink disease*) is the intoxication due to mercury which is manifested in neurological alteration, convulsion, vascular collapse, and diarrhea. The intoxication is caused by the presence of mercury concentrations higher than the reference levels in estuarine, lagoon, and lake waters, mercury that, being fixed by fish, can enter the food chain. Hg intoxication may also be related to dental amalgam.

Mercury is a heavy metal that is liquid at the normal ambient temperature, and its melting point occurs at −39 °C, which is why it can be solid at very low temperatures. Mercury occurs in the terrestrial crust with an average concentration between 53 and 56 ppb (parts per billion, being 1 ppb = 1 $mg.t^{-1}$). The main mineral of Hg is *cinnabar* (HgS).

The main natural sources of mercury are volcanic eruptions, while the main anthropogenic sources of mercury are the combustion of fossil energy resources, coal, oil, and natural gas, as well as pharmaceuticals, paper and pulp preservatives, agriculture industry, and chlorine and caustic soda production industry (Morais et al. 2012). Another source of mercury, whose harmful effect on human health in the central nervous system continues to be a source of controversy, is the so-called amalgam consisting of mercury (about 50%), lead (Pb), silver (Ag), copper (Cu), zinc (Zn), and tin (Sn), which had been widely used in the obliteration of dental caries. Mercury is released from dental amalgam in the vapor state. Although the dental amalgam has been used for more than 100 years, the media has recently emphasized the 8-year experimentation of 253 young people at Casa Pia, a cooperative experimentation between the University of Washington (USA) and the Faculty of Dental Medicine of Lisbon. The results of this experimentation remain unknown.

Possible risks to the environment have already banned thermometers, barometers, and pressure gauges (blood pressure meters) that worked with mercury.

The toxicity of mercury depends on the chemical species in which it occurs. When it is presented as a metal (Hg°), it is very volatile at room temperature and can be inhaled, penetrating first into the lungs and then into the blood. Mercury has the ability to combine with other elements and form organic and inorganic mercury (Alina et al. 2012).

Cinnabar also called zhusha in Chinese is a key sedative component of many Chinese medicines.

Hg toxicity depends on its chemical form (ionic, metallic, and organic), the least and the highest toxicity being attributed to the ionic and to the organic forms, respectively (Clarkson 2006). Organic Hg compounds easily pass across biomembranes and are lipophilic, the reason why the highest Hg concentrations are found in the liver of fatty fish species.

Mercury and its compounds are highly toxic, especially methylmercury – a potent neurotoxin. Hg is widely dispersed through the atmosphere and is biomagnified through the food chain. Minamata disease, the name given after methylmercury was found in the seafood in Minamata and Niigata, in Japan, in the 1950s–1960s, caused the death of thousands of people. Mercurial fungicides treated wheat seeds caused poisoning and death of 5000 to 50,000 people (Mudgal et al. 2010). Tokuomi et al. (1977) were the first to describe the symptoms of methylmercury poisoning.

According to the WHO (World Health Organization), in the human body, there is no more than 2000 ng (nanogram) of Hg/g, while for the American Environmental Protection Agency, the maximum drops to 1000 ng Hg/g (WHO 2004a, b).

Finally, a number of recent scientific articles of a general nature are mentioned among the many articles found in the literature related to the toxicity of mercury: Chan and Egeland, 2004; Kazantis, 2004; Bernhoff, 2012; and Genchi et al., 2017.

4.7.3 Cadmium (Cd)

Cadmium (Cd) occurs at the Earth's crust at an average concentration of 0.1–0.5 ppm. The highest concentrations of Cd are associated with the deposits of zinc, copper, and lead sulfide minerals. Cd is a byproduct of Zn production. Cadmium has many important applications, such as in batteries, pigments, plastics, and metal coatings, and is widely used in electroplating (Martin and Griswold 2009).

Acid soils rich in organic matter facilitate the incorporation and accumulation of Cd, of natural or anthropogenic origin, in plants, particularly severe when they are edible by humans and other animals.

Fertilizers, port activities, effluent from certain industrial activities, and effluents from domestic waste treatment plants, urban traffic, etc., are responsible for the anomalous concentrations of Cd in the soil and water. Cd and its compounds are highly soluble in water compared to other metals which explains its high bioavailability and bioaccumulation. Cd may be present as water-soluble salts in the form of chloride, sulfate, and nitrate.

Cadmium has been classified by the International Agency for Research on Cancer (Henson and Chedresse 2004) as a carcinogen of Group 1 for humans, particularly affecting the lungs, prostate, and kidneys. Osteoporosis is a critical effect of Cd exposure. Cd gets preferentially absorbed in the lungs and less in the gastrointestinal tract. Man's exposure to Cd occurs as a result of natural processes and man-made processes (combustion of fossil energy resources and other industrial activities). Cd is released to the environment through natural activities, such as volcanic eruptions and weathering, and human activities, such as mining, smelting, tobacco smoking (tobacco plants can accumulate Cd from the soil), incineration of municipal waste, and manufacture of fertilizers. Cd can cause both acute and chronic intoxications (Chakraborty et al. 2013).

Very recently Suwatvitayakorn et al. (2020) report the result of studies of the human health risk assessment of Cd exposure through rice consumption in cadmium-contaminated areas of Mae Tao watershed, Tak, Thailand. The authors found out in locally grown rice, the main agricultural product locally consumed, Cd concentrations in the range within 0.01–7.75 mgkg^{-1}, mostly higher than the Codex maximum standard of Cd in rice (0.4 mg.kg^{-1}) (IWMI 2005), whereas soil Cd concentrations range within 0.1–284 mg.kg^{-1}, mostly over the EU maximum standard level of 3 mgkg^{-1} for the soil (IWMI 2005). Potential health risk (HQ) naturally increases with rice ingestion rate.

Cd is an environmental pollutant that is closely linked to cardiovascular diseases (e.g., atherosclerosis) (Angeli et al. 2013). Toxic effects of Cd on humans are reported by authors such as Flick et al. (1971), Norberg (2009), and Jarup and Akesson (2009). It is in the respiratory, circulatory, and metabolic systems that deleterious effects are felt in humans (WHO 2010a).

In October 2017, the European Parliament approved a commission draft which limits the Cd content to 60 mg/kg in phosphate agricultural fertilizer, which after 3 years would be reduced to 40 mg/kg and would continue to be reduced to reach 20 mg/kg after 12 years. In Finland and Hungary, the current limit is already 20 mg/kg.

The largest reserves of sedimentary calcium phosphate (*carbonate apatite* where Cd substitutes Ca) are in Morocco (50,000 million tons) with an average Cd content estimated at 55 mg/kg. In the equally sedimentary calcium phosphate of Tunisia and Algeria, the levels of Cd can reach the values of 90 mg/kg.

Intoxication with Cd is called *cadmiosis*.

4.7.4 Antimony (Sb)

Antimony is a silvery white naturally occurring metalloid element that occurs in very low concentrations in the Earth's crust and in two oxidation states, 3^+ and 5^+.

Metallic Sb and a few trivalent Sb compounds are the most significant regarding exposure potential and toxicity. Intoxication with Sb is called *antimoniosis*.

Some antimonials such as antimony potassium tartrate (APT) have been used medicinally as parasiticides.

Sb is nutritionally not essential and no metabolic function is known. Sb_2O_3 is being used as a catalyst (e.g., in the manufacturing of polyethylene terephthalate (PET) used for container closure system components.

Sb and Sb_2O_3 have low solubility in water, whereas ATP is water-soluble.

4.7.5 Arsenic (As)

Arsenic (As) is a metalloid that occurs in several minerals, sulfides in particular, as a major element or trace element. The average content of arsenic in the terrestrial crust is about 5 mg.kg^{-1}.

Smedley and Kinniburgh (2002), Mandal and Suzuki (2002), and Ravenscroft et al. (2009) report the distribution of arsenic globally. Bowell et al. (2014) report and discuss the environmental geochemistry of arsenic. This element was first described by Theophrastus in 300 B.C. and named it arsenikon, and only in the thirteenth century, the alchemist Albertus Magnus was able to isolate the element from the mineral *orpiment*, an arsenic sulfide (As_2S_3).

Arsenic is usually associated with gold, lead, zinc, tin, nickel, and cobalt in sulfide deposits, and it could be released to the environment during the mining works and processes. Arsenic occurs as a major constituent in more than 200 minerals, most of them ore and their weathering products. These minerals are relatively rare in nature but are more concentrated in particular ore zones. The most abundant As ore minerals are *arsenopyrite* (FeAsS) and *arsenic pyrite* $Fe(S,As)_2$. Arsenic has many applications: wood preservation, pyrotechnics, light-emitting diodes, lasers, and pesticides.

It has been documented that, in 1955, in Japan, As was accidentally mixed into the Morinaga powdered milk “MF”, as a result of which 600 newborn babies died and 624 were afflicted by severe mental retardation, development difficulties, and brain damage-related paralysis (Mudgal et al. 2010).

Numerous cases of *arsenicosis*, i.e., poisoning with *arsenic*, have been identified in India and Bangladesh, originating from the consumption of water from wells that cross rocks with *arsenical pyrite* $Fe\ (S,\ As)_2$. Arsenic contaminations can occur as a result of both natural geologic processes and the activities of man. Anthropogenic sources of arsenic include human activities such as mining and ore processing; the smelting process can release arsenic to the air and soil. Groundwater contamination is caused by arsenic-bearing minerals existing in the geologic reservoir or aquifer. Arsenic in small doses was used to improve fitness and was also used as a poison.

The As forms complexes with sulfur (S) such as *red arsenic* (As_4S_4 or As_2S_2) also called *realgar*; the *yellow arsenic* (As_2S_3) also called *orpiment* or *auripigmento*; and *white arsenic* (As_2O_3) also called *arsenicum album* and *arsenolite* which is produced by heating *realgar*. These As compounds have been known as venom since antiquity, yet their medicinal use is registered in the *Hippocratic Corpus* and among traditional Chinese drugs.

The empirical use of arsenic has been a tradition in Chinese medicine, but it should be noted that in contemporary China, scientifically based, As_2O_3 has been used successfully in the treatment of leukemia, a lethal hematological disorder. *Realgar* also called xionghuang in Chinese is used to treat various diseases (mouth and tong ulcers, vertigo, and sore throat) and shows promising anticancer activity in combination with other medications (Wang et al. 2008; Zhang et al. 2009; Wu et al. 2011).

The benefits and risks often go hand by hand. To save a life from cancer, the use of toxicants like arsenic could be justified (Wu et al. 2011). Recent studies have indicated that *realgar* has an obvious anticancer effect in the clinic, especially on hematological cancer. *Realgar* research has been applied to the inhibition of the functions of acute promyelocytic leukemia (APL) and chronic early young granulocyte leukemia (CPL) (Samuel and Kenneth 2001). However, realgar is one of the mineral agents with poor solubility. And it has been known as poisons since ancient times. Modern medical research demonstrated that long-term realgar intake will cause severe liver and kidney damages (Liu et al. 2008).

Currently, according to Chen et al. (2017), realgar has confirmed antitumor activities, both in vitro and in vivo, through the induction of apoptosis of realgar extracted using *Acidithiobacillus ferrooxidans* (*A. ferrooxidans*). *Realgar* is characterized by high toxicity, poor availability, and low solubility. To overcome *realgar* low solubility bioleaching, a new technology to greatly improve the use rate of arsenic extraction from *realgar* using bacteria is a novel methodology that addressed a limitation of the traditional method for realgar preparation. The bacteria obtain energy by oxidizing ferrous ions and elemental sulfur. Bioleaching provides higher efficiency and safety than raw *realgar* powder and other arsenic compounds.

According to Smedley, drinking water constitutes a major and possible, dominant pathway of exposure to arsenic in humans. The actual WHO provisional guideline value for arsenic in drinking water is 10 μg/L, having been reduced from 50 μg/L in 1993. Most industrialized countries also take 10 μg/L as a reference limit.

Arsenic at much higher concentrations (sometimes 30–50 times) than the recommended maximum value (10 micrograms/liter) has been found in certain spring waters or in waters collected, through boreholes, in underground aquifers which circulate in rocks containing arsenic sulfides such as *arsenopyrite* (FeAsS) and *arsenian pyrite* (FeS_2). This is the case, in Portugal, of the waters consumed in certain places of the municipalities of Baião, Valbom, Vila Flor, and Ponte de Sor.

The effects of arsenic toxicity on human health have been investigated by several authors such as Saha et al. (1999), Fazal et al. (2001), Alam et al. (2002), Bissen and Frimmel (2003), Ng et al. (2003), Kapaj et al. (2006), Kazi et al. (2009), Jaishankar et al. (2014), and Singh et al. (2015).

Humans are exposed to arsenic by means of air, food, and drinking water. Arsenic (As) ingestion in humans through various food sources is a worldwide health issue. Rice is a major dietary source of inorganic As, particularly for people living in As-endemic areas of China, Bangladesh, Japan, Cambodia, India, Vietnam, and Thailand (Huang et al. 2015; Kwon et al. 2017; Meharg et al. 2008).

Kuwarathilaka et al. (2019) have evaluated the major causes for high inorganic As levels in cooked rice foods and the potential of post-harvesting and cooking options for decreasing inorganic As content in cooked rice, focusing particularly on As-endemic areas. The authors found out that the key factors for high As concentration in cooked rice in As-endemic areas are as follows:

1. Rice cultivation on As-contaminated paddy soils
2. Use of raw rice grains which exceed 200 μg kg^{-1} of inorganic As to cook rice

3. Use of As-contaminated water for cooking rice

In vitro and in vivo methods can provide useful information regarding the bioaccessibility of *arsenic* (*As*) in the gastrointestinal tract. Rice grains in As-endemic areas can contain over 90% of inorganic As, i.e., arsenite As(III) and arsenate As(V), and the rest are organic As species. The intake of inorganic *arsenic* is a recognized cause of cancers of the skin, lungs, and bladder and a potential cause of noncancerous health outcomes including respiratory, cardiovascular, neurological, and metabolic diseases (Sanchez et al. 2016).

Drinking water contaminated with As is one of the major causes for arsenic toxicity in more than 30 countries in the world (Chowdhury et al. 2000). Hoque et al. (2011) state that if the As content in the groundwater is 10–100 times the value given in the WHO guideline for drinking water, 10 μg/L, it could be a threat to human health.

Arsenic toxicity can be either acute or chronic, and in the last case referred to is called *arsenicosis*. Pigmentation and keratosis are the specific skin lesions that indicate arsenicosis (Martin and Griswold 2009). The toxic effects of arsenic much depend on chemical species and oxidation state. Inorganic As is considered carcinogenic and may cause lung, kidney, bladder, and skin disorders. Drinking water is one of the primary routes of exposure to inorganic arsenic (Mudhoo et al. 2011). Several investigators, such as Chwirka et al. (2000), Iqbal et al. (2001), Sancha (2006), and Rahman et al. (2011), have studied and proposed technological processes for the removal of arsenic from underground drinking water.

Arsenic is a trace metalloid of high concern in China; its deficiency or excess exposure can cause endemic diseases. Endemic *arsenicosis* in China is induced from exposures to high arsenic concentrations, in either drinking water or domestic combustion of As-rich coals (Li et al. 2012).

The reduced form As^{3+} may be more toxic than the oxidized form As^{5+}.

In the sulfide mines of Aljustrel and Neves-Corvo, in Portugal, As-bearing minerals, *arsenopyrite* (FeAsS) and *tetrahedrite* $(Cu,Ag,Zn,Fe)_5(Sb,As)_4S_{13}$, are found.

4.7.6 Selenium (Se)

Selenium is a basic constituent of very rare minerals, such as $FeSe_2$ *ferroselite*, Cu_2Se *berzelianite*, and *clasuthalite* PbSe, and is a trace element in some sulfides such as the FeS_2 *pyrite*. In general, Se occurs in very small amounts in rocks and soils, but in certain rocks rich in phosphates, sulfides, organic matter, and coals, it can occur in appreciable concentrations. The average concentration of Se in the land crust is 0.05 ppm. In soils the concentration of Se varies between 0.1 ppm in very deficient soils in Se and 1200 ppm in soils rich in organic matter.

Volcanic activity is the main source of Se, and concentrations of several hundred of ppm may occur in soils of volcanic territories. The Se is incorporated into humans through the consumption of edible plants and water. Certain species of plants have particular affinity to Se being able to make its accumulation.

The toxicity of Se in the soil depends on its bioavailability, higher in alkaline soils, lower in acid soils. The Keshan and Kashin-Beck diseases, identified in certain regions of China, were attributed to soils and waters very deficient in Se, and endemic selenosis has been identified in areas with high Se concentrations in soils derived from Se-enriched black carbonaceous siliceous rocks and carbonaceous shale and slate (Li et al. 2012).

In turn, the excess of Se in plants and water can cause the disease called *selenosis* that is attributed to the deficiency and excess of selenium (Se).

Selenium is a very rare metal in nature, but in increased levels, it is often more disturbing than its deficiency, since deficiency can be offset by the introduction of adequate doses of Se in diets. The concentration of *selenium* in most rocks and soils is less than 0.1 ppm, other rocks bearing minerals that are sulfides and in soils from them derived significantly higher concentrations may occur.

The death of and malformations identified in fish and ducks living in the waters of Kesterson Wildlife Refuge lagoons that received the runoff waters that leached the soils of the agricultural lands of the San Joaquim Valley in California were attributed to the high levels of Se.

Se deficiency is known to cause disease in humans, as is the case of Keshan disease, identified, for example, in the regions of Southeast China, where soils are deficient in Se. It is also known that excess Se causes health problems, but fortunately, occurrences of soils with relatively high levels of Se, toxic to plants and animals, are rare. *Selenium* (Se) is a micronutrient trace element that has a strong antioxidant power, and protecting the cells against the so-called free radicals can prevent its deterioration and aging.

4.7.7 Thallium (Tl)

Thallium is a trace element extremely toxic that could cause chronic and acute poisoning called *thallotoxicosis* (Smith and Carson 1977). Thallium, a metalloid, is widely distributed in the natural environment but generally is present in low concentration, with 0.75 mg/kg in the Earth's crust (Taylor and McLennan 1985), 0.01–3 mg/kg in soil (Fergusson 1990), 0.001–0.25 μg/L in water (Banks et al. 1995), and 0.03–0.3 mg/kg in food crops (Kabata-Pendias and Pendias 1992).

A typical serious endemic *thallotoxicosis* has been identified in southwestern China, more precisely in the rural area of Lanmuchang, in the Guizhou Province, with sources in polluted drinking water and food related with soils developed in mineralized Tl-bearing sulfide minerals (Li et al. 2012).

Thallium minerals are extremely rare; *lorandite* (TlAsS) was identified in the area referred to (Chen 1989). In the 1960s–1980s, Lanmuchang with about 1000 inhabitants was found to be affected by the endemic *thallotoxicosis*, the symptoms being hair loss, reduced vision, and blindness (Liu 1983; Zhou and Liu 1985; Long and Zhang 2005), with causes being attributed to Tl contamination of drinking water and edible vegetables. As a matter of fact, high concentrations of Tl were found in the soil, groundwater, and food crops. The estimated ingestion rate of Tl is 1000 times higher than the world average daily intake (2 μg/day) as indicated by Sabbioni et al. (1984). Since the early 1990s, Tl-poisoning was much attenuated through the supply of Tl-free water piped from outside Lanmuchang area. However, the symptoms of Tl intoxication still persist because some villagers for agricultural and domestic uses utilize natural water sources, from dug wells and springs (Xiao et al. 2003, 2007).

4.7.8 Fluorine (F)

Fluorine (F) is one of the most abundant trace elements in the terrestrial crust, with a mean content of 625 mg/kg (Edmunds and Smedley 2005). *Fluorine* is the most electronegative element and chemically reactive of all halides; it occurs in the ionic form of *fluoride* (F^-) in the water (Hem, 1985) as well in minerals and may be beneficial or toxic to humans and other animals (Dissanayake 1991; Ozsvath 2009) depending on the daily intake.

Drinking water is the main source of F^-. The easy exchange of the ion F^- (1.36 Å) with the ion OH^- (1.40 Å) facilitated by the similarity of ionic radius enables F^- to quite easily enter into the aqueous medium. Also, it can easily exchange the OH^- groups in clay minerals from soils and clays. Hence groundwater, soil, and clay are the media where the highest fluoride concentrations can be found (Table 4.5).

Assuming that an adult drinks on average 2 liters of water/day, the intake of F^- should not exceed 3 mg/day (1.5 mg/L) (WHO 1994). The guideline for F^- in drinking water depends on the temperature, ranging from 0.4–0.7 mg/L in South Africa (Muller et al. 1998), 1 mg/L in China and India, and 0.8 mg/L in Algeria.

Endemic diseases, *dental fluorosis* and *skeletal fluorosis*, caused by high levels of F^- (>1.5 mg/L) that can reach values between 10 and 60 mg/L, have been reported in several countries: China, India, Canada, Turkey, South Africa, Morocco, Algeria, Egypt, Tunisia, Nigeria, Tanzania, Senegal, and Cameroon.

Fluorite (CaF_2) and *fluorapatite* ($Ca_{10}(PO_4)F_2$) are the major fluoride minerals. Fluoride also occurs as a trace element in the *phyllosilicates*, particularly in the

Table 4.5 Human health impacts of fluoride

Fluoride concentrations	Health impacts
Nil	Limited growth and fertility
0–05 mg/L	Dental caries
0.5–1.5 mg/L	Healthy teeth
1.5–4.0 mg/L	Dental fluorosis (mottling of teeth)
4.0–10.0 mg/L	Dental fluorosis, skeletal fluorosis
10.0 mg/L	Crippling fluorosis

biotite mica ($K(Mg, Fe^{+2})_3(Al,Fe^{+3})Si_3O_{10}(OH,F)_2$) where F^- replaces OH^-, and in *clay minerals* $(OH,F)_2$ and also in the double-chain *inosilicates* represented by the amphiboles of formula $X_2Y_5(Si,Al)_8O_{22}(OH,F)_2$, where X may be Mg, Ca, and Fe or Na and Y may be Mg, Fe, and Al.

The dissolution of F^- of the silicates is favored by alkaline pH, anion exchange ($OH^-$by F^-), and the residence time of the groundwater in the aquifer.

In addition to the natural sources of F, there are also anthropogenic sources, such as phosphate fertilizers used in the aquifer recharge area and the gaseous emissions produced in ceramic plants.

Fluorosis is caused by the presence of *fluoride* concentrations higher than the reference concentrations (1 ppm/liter or 1 mg/kg) in certain drinking and tooth- washing waters (*dental fluorosis*, Fig. 4.5), or skeletal (*skeletal fluorosis*). It is also known that *fluoride deficiency* in water provides the appearance of dental caries, which is why it is sometimes necessary to introduce fluoride into the drinking water deficient therein and even into toothpastes.

Fluorosis, an illness due to the intake of excess *fluoride*, has yet to be treated and is considered a deadly disease. Nevertheless, the *fluoride* ion (F^-) strengthens the bones and contributes to avoid dental caries, which is a most prevalent infectious disease in the world that mainly affects children and young people, and is highly conditioned by oral hygiene since certain bacteria, such as *Streptococcus sobrinus* (*S. sobrinus*) and *Streptococcus mutans* (*S. mutans*), are considered the main etiological agents of dental caries.

Fluoride, as a rule, occurs at relatively low levels in rocks and soils, but in case they are rich in minerals bearing F^-, such as *biotite*, also called mica black concentrations of F^- may be high enough and when these minerals are dissolved the released F^-may be incorporated into the water of confined underground aquifers and may cause *dental fluorosis* and *skeletal fluorosis*. However, concentrations of F^- in the water that are not greater than 1 ppm or 1 $mg.kg^{-1}$ are known to be good for the bones and teeth.

The air is another *fluoride* vehicle that originates in certain industrial activities, such as ceramic and glass, which can cause fluorosis. In ceramic plants, clay and other raw materials are burned at temperatures generally as high as 1000 °C, producing gaseous emissions consisting of H_2O, CO_2, SO_3, and H_2F. The existence of F^--containing aerosols around the chimneys of ceramic factories is not only dangerous for man but also for other animals and plants. Also, in ceramic plants, it is often possible to see the windows corroded by H_2F, and around these factories, the effects of acid aerosols can be appreciated in the plants and trees. SO_2 emitted by ceramic plants and resulting from the firing of clay (clay deposited in estuarine and marine environments usually contains sulfides and sulfates), or from burning of fuel, fuel, or natural gas, accentuates the acidic character of aerosols.

Fluoride, is particularly deleterious to herbivorous animals. Fluoride-rich patches cause either *fluorosis* disease expressed as skeletal malformations or paralysis disease expressed by the loss of sensation and autonomy of movement. More than 30–50 ppm fluoride determined in forage can cause serious health problems to livestock. Even higher concentrations of fluoride can be found in vegetation located around the chimneys of ceramic factories.

The mean F^- content determined in clays is estimated to be 0.01–0.02%, with F^- concentrations being much higher in *illite*- and *smectite*-rich clays than in *kaolinite*-rich clays. The mineral *biotite*, that is, *ferromagnesian mica*, as a rule, carries more F than the mineral *muscovite*, that is, an *aluminous* and *potassium mica*. The F content in *biotite* can reach values around 2%, the F being isomorphously replacing OH groups in the ferromagnesian mica structure.

During the firing of the clay-based ceramic products at a temperature higher than the temperature at which the F becomes free, the fluorine is emitted into the atmosphere of the furnace from where it passes through the chimney to the outer atmosphere of the plant. The temperature at which the F emission occurs depends on the nature of the F-bearing minerals, ranging between 500 and 700 °C for kaolinites and smectites and between 700 and 900 °C for illites and micas. The fluorine ion released after combining with the humidity of the air inside the furnace produces hydrofluoric acid (HF) which is drawn by the gaseous stream flowing above.

The fluoride negative effects on vegetation could be observed around the ceramic plants using as raw material the illitic/smectitic clays of the Upper Cretaceous Aveiro-Ilhavo-Vagos geologic and stratigraphic unit that occurs in the region of Aveiro, Portugal, are used in the manufacture of brick, floor tile, wall tile, and roof tile. Such clays contain levels of F variable between 1000 and 2000 ppm or $mg.kg^{-1}$, and only about 50% of these contents are emitted into the atmosphere during the ceramic firing process. The Cl and S that may be also present in the composition of these clays which had been deposited in an estuarine medium will participate too in the composition of the gaseous emissions resulting from the ceramic firing process.

On the other hand, mineral water, particularly groundwater, is another F^--dissolved vehicle from the regional rocks where F-bearing minerals are present, such as *fluorapatite* ($Ca_5(PO_4)_3F$) and *fluorite* (CaF_2).

The medical advice adopted and expressed in the World Health Organization (WHO) reference recommendations is that drinking water should not contain more than 1.5 ppm F and the optimal concentration of F should be very close to 1 ppm. F concentrations somewhat less than 1.5 ppm help to prevent tooth decay and the development of a perfect bone structure in humans, in particular, and in animals, in general. *Fluoride* doses above 1.5 ppm accentuate the strong development of brown spots on the teeth and the consequent degradation and, on the other hand, induce the prevalence of *osteoporosis* and the collapse of the vertebrae (Sharma 2003).

The reference values recommended by the World Health Organization (WHO 1993) for the chemical elements in drinking water which may be harmful are as follows: Pb (0.01 mgL^{-1}), As (0.01 mgL^{-1}), Fe (0.30 mgL^{-1}), Cr (0.05 mgL^{-1}), nitrates (50 mgL^{-1}), nitrites (0.5 mgL^{-1}), Al (0.2 mgL^{-1}), Mn (0.05 mgL^{-1}), sulfates (250 mgL^{-1}), chlorides (250 mgL^{-1}), and ammonia (0.5 mgL^{-1}).

The World Health Organization (WHO) believes that our health depends on 50% of food, 20% of the environment, 20% of the genome, and 10% of medical care. Drinking water is the main product consumed at the rate of 1.5–2 liters per day, and, as it is part of the environment, its quality depends a lot on this medium. For example, in the island of Porto Santo from the Madeira archipelago, *dental fluorosis* and *skeletal fluorosis* are endemic. They are essentially due to the excessive concentration of fluoride in the water of local springs that is consumed by the inhabitants. Silva (2003) shows for the mineral water of two springs, Morenos and Zimbreiro, *fluoride* contents of 3.95 ppm and 1.90 ppm, respectively, values significantly higher than the recommended maximum value (1.5 ppm) by the World Health Organization (WHO). The water of both Morenos and Zimbreiro springs is classified as chloride-sulfate sodium water with relatively high TDS values, 1777 and 1960 mg/L.

Figure 4.5 shows the image of *dental fluorosis* revealed in an individual well identified who lives in the island of Porto Santo.

The soils in large areas of Porto Santo also show fluoride anomalies, particularly the residual soils developed on the upper Miocene hyaloclastic tuff that, due to submarine alteration in a first phase and subaerial alteration in the later phase, produced bentonite deposits. The clay mineral, *dioctahedral smectite*, is the main component of *bentonite*, whereas *fluorapatite*, $Ca_5(PO_4)_3F$, and *titanomagnetite*, $Fe^{2+}(Fe^{3+},Ti)_2O_4$, in which Ti^{4+}substitutes some Fe^{3+} isomorphously, are accessory minerals of *bentonite*.

Of the four degrees of *dental fluorosis* established in 1938, the example shown in Fig. 4.5 may be classified into grade 3 (*moderate fluorosis*).

Fluoride can be applied topically since 1955 when $Ca_2P_2O_4$-associated SnF_2-containing toothpaste has been introduced on the market and is considered to have good cariostatic action. Other minerals such as sodium metaphosphate, calcium pyrophosphate, calcium carbonate, aluminum hydroxide, and dehydrated silica gel participate in this type of dentifrices acting as abrasives. At present, *fluoride*-bearing dentifrices account for about 98% of all commercially available dentifrices. There are also *fluoride* solutions (mouthwash) based on sodium fluoride that are used to wash the mouth. Considering that the optimal F concentration in the drinking water

Fig. 4.5 Evidence of *dental fluorosis* in an inhabitant of the island of Porto Santo where water from some springs has fluoride concentrations of 3–4 ppm/liter. (Photo by João Baptista Pereira Silva, included in the book "Minerals and Human Health: Benefits and Risks", 2006, whose authors are Celso Gomes and João Silva)

is 1 ppm, the recommended fluoride supplement for that same water should not exceed 0.7 ppm.

The dosage of F^- supplements, as a rule, follows the recommendations proposed by the American Dental Association (ADA).

Very recently, Rasool et al. (2018) present an overview of *fluoride* contamination in groundwater. According to the authors, about 200 million people in 25 nations, particularly India, China, Pakistan, and Bangladesh, are exposed to toxicity by high concentrations of *fluoride* present in the water they ingest from underground aquifers.

Exposure to high concentrations of fluoride over long periods of time causes adverse health effects such as skin lesions, skin discoloration, cardiovascular affections, and *dental* and *skeletal fluorosis*. Also, in recent years, several studies have been published on the origin and impacts on human health of *fluoride* in groundwater, such as Fawell et al. (2006), Ayoob and Gupta (2006), Maheshwari (2006), Meenakshi and Viswanathan (2007), Pauwels and Ahmed (2007), Brindha and Elango (2011), Dar et al. (2011), Bashir et al. (2013), Edmunds and Smedley (2013), Vithanage and Bhattacharya (2015), and Srivastava and Lohani (2015).

In order to reduce the concentration of *fluoride* in contaminated water, several studies have been carried out and several technologies have been used: Azbar and Turkman (2000), Maheshwari (2006), Parmar et al. (2006), Meenakshi and Viswanathan (2007), Viswanathan and Meenakshi (2009), Thakre et al. (2010), Brindha and Elango (2011), Yin et al. (2015), Vithanage and Bhattacharya (2015), and Bibi et al. (2015).

4.7.9 Aluminum (Al)

Although the knowledge of the pathophysiology of Alzheimer's disease has greatly progressed over the past several decades, its causal mechanisms are far from clear. The hypothesis that aluminum exposure is etiologically related to Alzheimer's disease has led to much debate. The possibility of such a relation was suggested by the presence of aluminum in senile plaques and neurofibrillary degeneration, two histologic lesions that are the characteristic of the disease.

Several studies have found that intake of aluminum (El-Rahman 2003) increases the expression of amyloid protein in rodent tissues, a step that may be critical to the development of Alzheimer's disease.

Ecologic studies have suggested that the concentrations of aluminum in drinking water of 0.1–0.2 mg/L may increase the risk of Alzheimer's disease, with relative risks or odds ratios ranging from 1.35 to 2.67 (Rondeau et al. 2001; McLachlan et al. 1996). However, the epidemiologic studies conducted thus far have generally ignored individual daily intake of drinking water.

Rondeau et al. (2008) found out that high consumption of Al from drinking water may be a risk factor for Alzheimer's disease. The authors had examined the associations between the exposure to aluminum or silica from drinking water and the risk of cognitive decline, dementia, and Alzheimer's disease among elderly subjects followed for 15 years (1988–2003). They actively searched for incident cases of dementia among persons aged 65 years or over living in 91 civil drinking water areas in southern France.

Guyonnet et al. (2007) consider that silica present in drinking water bearing high Al concentration may be protective with respect to the decrease of cognitive function due to Al as it has been suggested by several epidemiological studies. It looks like that Al is deleterious when Si is low.

4.7.10 Radioactivity and Radon (Rn)

Radioactivity is a property that atoms of a certain chemical element have to emit electromagnetic radiation and particles from their unstable nuclei in order to gain stability. This emission of particles (alpha, beta, and gamma) causes a radioactive atom of a particular chemical element to become an atom of another chemical element.

Uranium (U), thorium (Th), and radio (Ra) are radioactive chemical elements that are present in certain minerals. The abundance of U in the Earth's crust is 2–3 ppm, while granitoids can reach 15 ppm. *Uraninite* (UO_2) and *pitchblende* (structurally disordered variety of *uraninite*) are the major uranium minerals. *Autunite* ($Ca(UO_2,PO_4)_2.8{-}12H_2O$), *torbernite* ($Cu(UO_2,PO_4)_2.8{-}12H_2O$), and *carnotite* ($K_2(UO_2)_2(VO_4)_2$) are other uranium-bearing minerals.

Uranium has three radiogenic isotopes: ^{234}U (0.006%), ^{235}U (0.72%), and ^{238}U (92.2%). The average life of the ^{238}U isotope is 4468 × 108 years being ^{206}Pb the final stable isotope.

Thorianite (ThO_2) and *thorite* ($ThSiO_4$) are the major thorium minerals.

From a toxicological point of view, U is harmful to living beings in the case where this metal or its decay products are to be incorporated into the human body in the form of uranyl, UO_2^{2+}. U can be present in several states of oxidation, U^{3+}, U^{4+}, U^{5+}, U^{6+}, and U^{4+} and UO_2^{2+} being dominant in the natural environment, particularly in groundwater. Among other effects, U overdoses cause acute renal failure and liver dysfunction.

Radioactivity was discovered, almost accidentally, by Becquerel in 1896 as he studied the phosphorescence of uranium salts. Indeed, the said investigator discovered the release of a new type of high energy radiation that was able to darken a photographic plate and that the rate of emission of the radiation was directly proportional to the amount of uranium present.

The radiation released in natural radioactivity can be separated or decomposed by an electric or magnetic field into three distinct types: alpha (α) radiation, beta radiation (β), and gamma radiation (Υ).

The natural radioactive isotopes have much practical importance for man. It is the case of the aforementioned radiocarbon or ^{14}C that is known to have a half-life of approximately 5730 years which may be used, for example, in the dating of certain geological and archaeological materials.

Isotopes are called the atoms of an element whose nuclei have the same number of protons but different number of neutrons, therefore different weight or atomic mass.

For example, the hydrogen element (H) has three isotopes:

The *prothio*, ^{1}H, which nucleus has one proton only
The *deuterium*, ^{2}H, which nucleus has one proton and one neutron
The *tritium*, ^{3}H, which nucleus has one proton and two neutrons

Another example is the element carbon (C) which has three isotopes: ^{12}C, whose nucleus has six protons and six neutrons; ^{13}C, whose nucleus has six protons and seven neutrons; and ^{14}C, whose nucleus has six protons and eight neutrons.

The term isotope means the same place, that is, the isotopes of the same element occupy the same place in the periodic table.

The study of the effects of radioactivity on human health only began after the end of World War II.

The so-called Nuclear Medicine is a specialized area of medicine that uses radioactive substances, the radioisotopes, to obtain an image of the human body, for the diagnosis and therapy of certain diseases, cancer in particular. The so-called imaging techniques used in Nuclear Medicine give physicians another way to see inside the human body by combining the use of radioisotopes, detectors, and computers.

Among the techniques mentioned, which allow the detection of tumors, aneurysms and various situations of inadequate functioning of organs and tissues, the following are noteworthy: positron emission tomography (PET), computerized photon emission tomography (SPECT), imaging cardiovascular, and bone imaging.

Certain bodies concentrate certain types of chemicals. For example, thyroid gland concentrates iodine, which can be detected by using radioactive iodine ^{131}I can and is used to treat certain thyroid cancers. Also, certain cancers concentrate phosphates, whereby the injection of the ^{32}P isotope into the bloodstream can detect the tumors by their increased radioactivity.

There are several radioisotopes used in Nuclear Medicine, all having rapid decays, from minutes to hours, and are eliminated in the urine and feces.

Drugs that carry the radioisotopes to the affected organs or tissues are called radiopharmaceuticals, compounds without pharmacological action that have a radionuclide in their composition and are used in Nuclear Medicine for the diagnosis and therapy of various diseases. For the diagnosis, radiopharmaceuticals are used which contain radiation-emitting radionuclides or β^{+}positron emitters, since the decay of these radionuclides gives rise to very penetrating electromagnetic radiation that passes through the tissues and can be detected at the exit.

For therapy the radiopharmaceuticals must include in their composition a radionuclide emitting ionizing particles α, β^{-}, or Auger electrons, capable of selective destruction of tissues (Oliveira et al. 2006). According to these authors, radiopharmaceuticals are classified into two types:

1. First-generation perfusion radiopharmaceuticals or radiopharmaceuticals that are transported through the bloodstream and reach the target tissue or organ
2. Specific radiopharmaceuticals or second-generation radiopharmaceuticals containing a biologically active molecule capable of binding to certain tissues or organs

The natural radioactive gas called *radon* can have negative impacts on human health. *Radon* is a chemical element of symbol Rn that occurs in the natural environment as a colorless, odorless, and tasteless gas, therefore undetectable by the human senses. *Radon* is a rare and noble gas that is a product of the decay of the radio element which in turn is a product of the slow and indirect decay of the radioactive elements uranium (U) and thorium (Th). *Radon* has several isotopes, with the ^{222}Rn isotope being the most stable, with a half-life of 3.8 days, which could be harmful to human health. According to the US Environmental Protection Agency (EPA), radon, following cigarette smoking, is the most frequent cause of lung cancer.

The isotope ^{222}Rn decays and produces new radioactive elements called children of *radon* that (Becker 1999; EPA 2005a) occurs in the solid state and can attach to surfaces, just as dust particles in the air adhere to the surfaces. Thus, when *radon* is inhaled, the children of *radon* adhere to the surfaces of the respiratory tract and the lung giving rise to the risk of developing cancer.

Epidemiological studies have shown a direct relationship between the inhalation of high concentrations of *radon* and the incidence of cancer (Steindorf et al. 1995; Pershagen et al. 1994). But even though it may be cancer-causing, *radon* can be used in radiotherapy treatments to control or kill malignant cells. Zdrojewicz and Strzelczyk (2006) published a rather interesting article about *radon* treatment controversy.

Some studies reported positive effects (Erickson 2007; Falkenback et al. 2005) on people suffering from chronic pain related to musculoskeletal disorders and who underwent treatments involving *balneotherapy* (with natural mineral water baths having radioactivity due to the radon it contains) or *speleotherapy* (with controlled time exposure inside underground galleries where the *radon* concentration is high, as in Montana radon health mine facilities, in the USA).

In Ukraine in the town of Khmilnyk, there are eight sanatoriums where around 50,000 patients are treated annually. Also, in Germany at the town of Schlema, there is a spa where radon treatments take place. It is classified as radioactive to water in which the radon concentration is greater than 64 Bq/L. In Portugal there are spas in the north and in the center of the country whose waters are radioactive.

The radon (Rn) concentration is measured in Becquerel (Bq) per cubic meter (Bq/m^3). In open or well-ventilated environments, radon concentrations range from 1–100 Bq/m^3, but concentrations in excess of 2000 Bq/m^3 may be present indoors. Generally, radon concentrations indoors are related with the geology of the regions, and granite regions often display the highest radon concentrations.

In Portugal and in Europe in general, the mapping of radon indoors was made, and the regions with occurrence of elevated radon concentrations are identified. Radon may accumulate in dwellings, caves, and mines and originate high radiation doses to residents and workers (Carvalho 2019). In Portugal, it is in inland regions of the center and north of the country where granite and schist dominate that radon concentrations are highest, particularly in places where uranium mineralization occurs.

The epidemiological study MinUrar (Uranium Mines and their Residues – Effects on Population) coordinated by the National Institute of Health Dr. Ricardo Jorge with the collaboration of the Technological and Nuclear Institute contemplated the analyses of soils, water, vegetables, blood, and human hair. The results of the study showed that there are high concentrations of radon (indoor *radon* concentrations are five times higher than the legal maximum) and heavy metals, particularly Pb and Po, in the municipality of Canas de Senhorim less mineralized adjacent counties.

The reduction in male fertility and changes in the functioning of the thyroid gland were attributed to radioactivity. Also, the number of deaths in the municipality of Canas de Senhorim attributed to cancers is higher than in the adjacent counties.

Urgeiriça miners have been subjected to radioactivity for years, not only in the mine they worked for but also in the houses built with the local mineralized rock and also through the water and vegetables they consumed. A program of decontamination (remediation) of soils and the homes of miners and relatives is underway.

The radioactive gas *radon* has been recognized as a carcinogenic agent. After tobacco, *radon* is a major cause of cancer. The World Health Organization (WHO) in order to reduce the incidence of lung cancer in the population proposed new limits to radon concentrations indoors that could be found in the *WHO Handbook on Indoor Radon: A Public Perspective* issued in 2009. This handbook is a key product of the WHO International Radon Project, which had been launched in 2005, and it is focused on residential radon exposure from a public health point of view and provides detailed recommendations on reducing health risks from radon and sound policy options for preventing and mitigating radon exposure. The material in the handbook reflects the epidemiological evidence that indoor radon exposure is responsible for a substantial number of lung cancers in the general population.

The new handbook indicates that radon exposure is a major and growing public health threat in homes and recommends that countries adopt reference levels of the gas of 100 Bq/m^3 (Becquerel per cubic meter). If this level cannot be implemented under the prevailing country-specific conditions, the WHO recommends that the reference level should not exceed 300 Bq/m^3.

Carvalho (2019) considers the worldwide need to get approved mitigation and preventive measures and suitable action plans to cope with *radon* exposures in the existing buildings and in the new constructions.

4.8 Sources and Pathologies Caused by Some Minerals *Strictu Sensu* (*s.s.*)

As a matter of fact, there are *minerals s.s.* on Earth that can be highly toxic to humans, either by themselves particularly due to their fibrous crystal habits or by the toxic metals and metalloids they contain.

The internet mentions the following as the ten most deadly minerals: *arsenopyrite* ($FeAsS$); *chalcanthite* ($CuSO_4.5H_2O$); *cinnabar* (HgS); *galena* (PbS); *chrysotile* ($Mg_3Si_2O_5(OH)_4$); *riebeckite* ($Na_2(Fe_3^{2+}Fe_2^{3+})Si_8O_{22}(OH)_2$); *hutchinsonite* ($(Tl,Pb)_2As_5S_9$); *orpiment* ($As_2S_3$); *stibnite* ($Sb_2S_3$); and *torbernite* ($Cu(UO_2)_2(PO_4)_2$ 8–12H_2O).

Chrysotile and *riebeckite* belong to a mineral group called asbestos, widely used for a variety of commercial and industrial applications thanks to its strong, fire-resistant, and flexible nature, and their thin fibrous crystals if respirable can cause lung cancer, mesothelioma, and asbestosis. *Arsenopyrite* is an iron arsenic sulfide; the oxidation of arsenopyrite leads to soluble arsenic in water and subsequent water pollution. *Chalcanthite* is a hydrated water-soluble copper sulfate; the copper being very bioavailable can be toxic to plants, and in high quantities is toxic to humans. *Stibnite* is the source of metalloid *antimony* (Sb), and stibnite paste has been used for thousands of years for cosmetics to darken eyebrows and lashes, as well as was to make eating utensils, causing poisoning from antimony ingestion. *Torbernite* releases *radon* (Rn) naturally and can cause lung cancer if exposure is long enough. *Cinnabar* is a deep red mercury sulfide mineral that provides much of the world's elemental *mercury* (Hg); when oxidized this element will produce methyl mercury and dimethyl mercury, two toxic compounds that can cause irreparable harm to the nervous system. *Galena* is the lead sulfide, the principal ore of *lead* (Pb), metal that if its intake doesn't get flushed out of the human body, it will be accumulated over the years, eventually reaching toxic levels. *Hutchinsonite* is an arsenic sulfide with *thallium* (Tl) and *lead* (Pb); thallium salts are nearly tasteless and highly toxic and have been used in rat poison and insecticides; exposure to it can potentially lead to death. *Orpiment* is an arsenic sulfide with a stunning orange-yellow color; this mineral strangely was once used medicinally in China despite its toxicity; the *arsenic* (As), especially if it is allowed to oxidize, will lead to arsenic poisoning if handled incorrectly.

Several diseases have been attributed to both the inhalation and the intake of toxic minerals being present, either in polluted air or in polluted water (Markov 2012; Das et al. 2019). In their very recent paper, Das et al. (2019) present an interesting review on the "Role of Toxic Metals such as Arsenic, Lead, Cadmium, Mercury, and Copper in Public Health and Cardiovascular Diseases." The review points out As, Pb, Cd, and Cu association with cardiovascular disease, and on the contrary, Hg was not significantly associated with cardiovascular risk.

Long-term exposure to high levels of toxic metals such as cadmium and arsenic has been associated with higher risk of cancer of the bladder, kidney, liver, lung, and skin (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans:

Arsenic, metals, fibers, and dust. IARC Monogr Eval Carcinog Risks Hum 2012, 100, 11–465).

Minerals *s.s.* and certain industrial products derived from airborne minerals in the form of dust, particularly those that can be classified as *nanominerals* – minerals with particle size measured in nanometers, being 1 nm = 10^{-9}m – may cause serious problems in the respiratory system.

Clay minerals can be classified as *nanominerals*. According to Wagner et al. (1998), the great majority of clay-based dusts, containing clay minerals, are innocuous, and therefore they only produce adverse effects if the exposure is intense and long-lasting. Among the clay minerals, only those with crystalline fibrous habits, such as sepiolite and palygorskite, are capable of causing lung tissue damage.

The World Health Organization (WHO) draws the attention of the Government Environmental Agencies to the need to carry out research aimed at assessing the real effects of mineral dust and also of aerosols and fumes in certain diseases and pathologies. Also, resulting from the interaction of water with certain types of rock and soil, water may contain high concentrations of metals and among them, heavy metals, e.g., copper, zinc, lead, chromium, cadmium and mercury, responsible for diseases, such as *Wilson's disease* or chronic liver disease due to excess buildup of copper in liver, *plumbism* or lead poisoning, and *hydrargirosis* or mercury poisoning, as well as metalloids, e.g., arsenic and fluorine which are responsible for *arsenicosis* and *fluorosis* diseases, respectively. All metals and metalloids referred to can be very harmful to human health.

Man is part of the natural environment, and, consequently, any aggression on the natural environment will affect himself, his quality of life and even his health. There are people who have professional occupations involving the exploitation of mineral resources in mines and quarries, which inhale mineral dust that can produce pathologies – *pneumoconioses* – of the respiratory system, such as *silicosis*, *asbestosis*, *berylliosis*, *siderosis*, *stannosis*, and *talcosis* caused by *crystalline silica*, *asbestos*, *beryl*, *iron oxides*, *tin oxides*, and *talc*, all of them potentially lethal. There is still another *pneumoconiosis* that affects coal workers. The history of mining goes back at least to Ancient Greece and Rome. Hazardous inhalation of mineral dust was recognized since then.

Pneumoconiosis, also called *fibrosis of the lung*, is a term used for the diseases associated with the inhalation of mineral dusts, either in the natural and general environment, or in the workplace as a result of industrial processes. *Pneumoconiosis* may be classified as either *fibrotic* or *nonfibrotic*, according to the presence or absence of lung fibrosis.

Chong et al. (2006), on the basis of thin sections on imaging observed by high-resolution computed tomography (CT), consider silicosis, asbestosis, talcosis, berylliosis, and coal worker pneumoconiosis examples of *fibrotic pneumoconiosis*. The same authors consider siderosis, stannosis, and baritosis as forms of *nonfibrotic pneumoconiosis*. The clinical diagnosis of *pneumoconiosis* is usually based on the occupational history of the patient and is followed by a standard chest radiograph. Magnetic resonance is a helpful imaging technique for distinguishing between progressive massive fibrosis and lung cancer.

Karkhanis and Joshi (2012) classified the occupational lung disorders according to the biological properties of the inhaled material into four main types:

1. Disorders caused by exposure to mineral dust;
2. Disorders caused by exposure to gases and fumes;
3. Disorders caused by exposure to organic dust;
4. Pulmonary and pleural malignancy caused by asbestos exposure causing pleural mesothelioma.

The severity of the lung disorder depends on the nature of the inhaled material and the intensity and duration of the exposure. If the number of inhaled particles is small, the alveolar macrophages converge upon extracellular particles and engulf them; if the number of particles is large, the elimination mechanism fails, ending up in the formation of lung nodules and fibrosis. The progression of the *pneumoconiosis* might occur, after the exposure cessation.

4.8.1 Silicosis

Silicosis also known as Potter's rot is the oldest recognized occupational disease that is caused by the inhalation of fine particles (0.001–0.005 mm) of crystalline silica generally in the form of quartz, SiO_2, a mineral very common in rocks such as granite and similar rocks extracted from quarries for ornamental purposes or for the production of brittle. Quartz is the major mineral present in the sands of desert regions.

Airborne quartz of micro-sized particles when inhaled are fixed in the lungs, obliterate the pulmonary alveoli, and cause extensive fibroses and emphysema that lead to the appearance of respiratory difficulties (dyspnea) and *pneumoconiosis* (a condition in which the lung tissue becomes rigid and loses ability to function), and can be lethal. The maximum level of exposure to the respirable dust of crystalline silica is set at 0.4 mg/m^3.

The inhalation of mineral particles present in aerosols and their deposition in the lung alveoli of man can cause health problems depending on the composition, size, and shape of the particles. Particles of silicates smaller than 5 μm ($1\ \mu m = 10^{-3}$mm) having fibrous habits generally penetrate deeper into the lungs than particles with larger size, which can become fixated and cause silicosis (due to the action of silica microcrystalline) or *asbestosis* (as a result of *asbestos* action).

Silicosis corresponds to a group of lung diseases that are caused by the inhalation of silica (SiO_2) if crystalline (quartz and the two other forms of crystalline silica, tridymite and cristobalite). *Silicosis* is a part of the silicotic diseases that are essentially occupational or occupational, related to activities where people are exposed to crystalline silica dust, such as mining and quarrying industry, cutting and finishing of siliceous natural stone, tunneling works in road and railway works, smelting of mineral concentrates for metal concentration, fragmentation and pulverization of siliceous rock, and preparation of raw materials for the manufacture of ceramics and glass.

Depending on the dose and the duration of the exposure, the silicotic diseases are classified into three grades or types:

1. *Chronic* or *ordinary* (means a low amount of free silica exposure for a period of around 20 years or more);
2. *Accelerated* (means higher amount of concentrated dust that was breathable, and the effects usually surface in a shorter period of time, 4–8 years);
3. *Acute* (means that patients would have the highest amount of exposure).

Fubini and Fenoglio (2007) in an article that deals with the toxic potential of mineral dusts highlight the differences in the toxic potential among airborne particles and describe what is known about the most notorious toxic agents, such as crystalline silica and asbestos. The authors consider that, besides crystal habit as the fibrous habit, crystallinity and surface reactivity are particle properties relevant to toxicity.

About the silica pathogenicity, important information can be found in the issue (volume 20/1 of 2001) of the *Journal of Environmental Pathology, Toxicology and Oncology*. In 1997, IARC (the International Agency for Research on Cancer) while classifying quartz and cristobalite in class 1, carcinogenic to humans, also stated that "carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs."

4.8.2 Asbestosis

Asbestosis is a pathology caused by *asbestos* also called *amiantos* (obsolete term), being both commercial terms used for mineral species of crystalline fibrous or acicular habit that belong to two subclasses of silicates: the *subclass of phyllosilicates* and the *serpentines group* being represented by its most common species *chrysotile* ($Mg_3Si_2O_5(OH)_4$) and the *subclass of inosilicates* and the *amphiboles group* being represented by its most common species, *actinolite* ($Ca_2(Mg,Fe)_5(Si_4O_{11})(OH,F)_2$).

The *serpentine group* comprises other mineral species which do exhibit platy crystal habits. The *amphibole group* comprises other species all exhibiting fibrous crystal habits such as *amosite* ($(Fe,Mg)_7Si_8O_{22}(OH)_2$), *crocidolite* ($Na_2(Fe,Mg)_3Fe_2Si_8O_{22}(OH)_2$), *tremolite* ($Ca_2Mg_5Si_8O_{22}(OH)_2$), and *anthophyllite* ($(Mg,Fe)_7Si_8O_{22}(OH)_2$). The *asbestos* belonging to the *serpentine group* have Mohs hardness estimated between 3 and 3.5, while the asbestos belonging to the *amphibole group* have Mohs hardness estimated as 5–6.

Asbestos were explored and used by humans for almost 4500 years. *Asbestos* clothes were mentioned by Charlemagne (742–814 A.D.) and by Marco Polo (1254–1324 A.D). The use of asbestos in an industrial scale was initiated in the 1850s (Carretero et al. 2013).

Fibrous *serpentines* are less dangerous to human health than fibrous amphiboles because of the smaller size and greater flexibility of their particles. The term *asbestos* derives from a Greek word meaning "inextinguishable."

Asbestos exhibits high thermal and chemical resistance, properties that justify the by humans from remote times in refractory materials and in electrical and thermal insulation materials. They also exhibit fibers or needles of variable size (10–50 μm in length and up to 3 μm in thickness) and chemically resistant which makes *asbestos* dangerous, because when inhaled they attach to the lung tissue causing *asbestosis* disease, which at the very least causes dyspnea (insufficiency respiratory failure) and, at the most, causes *fibrosis* or *pneumoconiosis*.

Cancer called *mesothelioma* of the pleural membrane that covers the lung may be a consequence of exposure to fibrous minerals, such as *asbestos*, and against it there is no treatment. Since *asbestos* carcinogenesis has been detected, leading to *asbestos* ban from important industrial applications based on specific properties, thermal (heat conductivity and refractoriness), and mechanical properties (high tensile strength), numerous studies have been carried out on the adverse health effects of fibrous minerals in general, not exclusively of *asbestos*, which comprise some minerals from the serpentine group and some minerals from the amphibole group, the first *phyllosilicates* and the second *inosilicates*.

In fact, in addition to the minerals of the *asbestos* group, there are other minerals that are also crystalline fibrous habits, such the inosilicate *wollastonite* ($CaSiO_3$), the zeolite *erionite* ($(NaK_2CaMg)1.5(Al_8Si_{28})O_{72}.28H_2O$), the phyllosilicates palygorskite ($(Mg,Al,Fe^{3+})_5(Si,Al)_8O_2(OH)_2\ 4(OH_2)$) (commercially known by the name *attapulgite*), and *sepiolite* ($Mg_8Si_{12}O_{30}(OH)_4(OH_2)_4.8H_2O$). In particular *erionite* is a class 1 human carcinogen and is best known from the epidemic of mesothelioma in Cappadocia, Turkey.

According to Buck et al. (2016), *naturally occurring asbestos* (NOA) is a designation used to describe fibrous minerals that include regulated *asbestos* as well as other fibrous minerals that do not meet the regulatory definition of *asbestos*, such as those referred to in the preceding paragraph.

Erionite has been also identified in North Dakota, USA, in sediments from the Arikaree Formation, sediments used as road gravel causing inhalation exposures to people performing road maintenance and to people driving on these roads (Pratt 2012; Carbone et al. 2011; Ryan et al. 2011). On the other hand, there are man-made fibrous materials, such as glass fibers, TiO_2 fibers, SiC fibers, and Si-Al ceramic fibers, whose interaction in human health in certain professions and environments needs to be investigated.

Although *asbestos* was recognized by the World Health Organization (WHO) as potentially carcinogenic materials in 1960, it was only several years later that they were banned from important industrial applications based on fire resistance and thermal insulation of these minerals.

In 1987, the most dangerous *asbestos* variety *crocidolite* was banned, and only very recently, in 2005, the variety considered less dangerous called *chrysotile* was banned. Usually cancer and other respiratory pathologies of the same genus as *asbestosis* as in the case of *silicosis* only manifest themselves after two decades of daily exposure. Prolonged exposure to *asbestos* can cause cancer of the esophagus, larynx, stomach, and intestines.

Asbestosis can be a professional disease, and the following occupational risk areas are civil construction, power plants, shipyards, blast furnaces, and air conditioning and ventilation.

In the second half of the last century, *asbestos* was widely used in building materials, such as *fiber cement* or *asbestos* cement applied to roofs of houses, schools, and other buildings, and still in the lining of heating and air conditioning ducts due to the thermal and electrical insulation properties of *asbestos*. This happened in Portugal from the 1960s until the 1990s of the twentieth century because *fiber cement* locally called *fibrocimento* is also a cheap and resistant construction material.

Asbestos cement, a mixture of cement with 10–15% of *asbestos*, as a rule the serpentine denominated *chrysotile* was very used in coverings of buildings and coatings of walls and ceilings. Also, the lining of the pipes where the building's heating fluids circulated was usually composed of asbestos materials. Over time, the deterioration of these materials, which usually takes place about 30 years after use, favors the release of the fibers into the interior atmosphere of buildings. *Asbestos* was also used as insulation material in boilers, false ceilings, and ducts in air conditioning systems.

In December 2005 the Portuguese mass media had reported a public health alarm caused by the occurrence of asbestos in certain public buildings daily frequented by many people, public servants and users of services. Within those public buildings, the Lisbon Justice Palace had been identified, being subjected to very complex and necessarily specialized interventions for the removal of the asbestos-containing materials wrapping the pipes used in the heating systems. Already between 1995 and 1998, 2400 m^3 of asbestos-bearing materials were removed from the roofs of the Beja Air Base hangars built by the Germans in the 1960s.

The world case, whose intervention for the removal of *asbestos* was more mediatic, corresponded to the Berlaymont building in Brussels, the seat of the European Commission which was closed in 1991 due to the high levels of fibers that were found to exist in the interior atmosphere and which only reopened in 2004.

Asbestos was recognized as a carcinogen in the 1960s by the World Health Organization (WHO), and since 2005, the European Union has prohibited the production and use of asbestos in construction materials, being obligation of member states through the Directive 1999, to identify the presence of asbestos in public buildings.

In Portugal, the DR, first series, no. 141 of 24 July 2007, makes the transposition of the Directive 2003/18/EC of the European Parliament and of the European Council of 27 March 2013. This directive defines the essential aspects for the health protection of workers against the risk of exposure to *asbestos* during work. It also defines the physical characteristics of respirable fibers: a length of more than 5 μm and a diameter of less than 3 μm, with a length/diameter ratio greater than 3:1, as well as the exposure limit value: 0.1 fibers per cm^3. Portugal still has not complied with this determination for public buildings, despite the 2011 law from the Republic Assembly that gave the Executive a 1-year deadline to complete the process.

In Portugal asbestos had been identified in 4263 public buildings, most schools, particularly the roofs of dining and gymnasium pavilions, are lined with *asbestos*-bearing “fibrocement” tiles, in some cases in an advanced state of degradation, naturally requiring the replacement of “fibrocement” tiles for other materials. In 2018, not more than 20% of those public buildings had been object of intervention. On 31 January 2014, an abnormally high number of people (19) affected by cancer (nine already deceased) were made public in a total of about 80 persons working in the building of the Directorate-General for Energy and Geology, in Lisbon, a situation that is being attributed to *asbestosis* and, as such, to be investigated.

Asbestos microfibers penetrate the human body through inhalation, and their accumulation can cause lung cancer known as *mesothelioma*. This disease usually appears between 15 and 40 years after the first exposure.

In vivo and in vitro experimental studies using certain animals and cell cultures and various types of fibrous minerals (*asbestos*, *sepiolite*, and *palygorskite* and fibers from man-made materials) have shown that tumor production is related to the size of the fibers and the time of residence in the lungs and not with the type of fibers, i.e., the crystal structure and chemical composition does not matter (Ishahara 2001; Kohyama 2005), although the in vivo and in vitro assay results do not always coincide.

For buildings and private homes, there is still no legislation applicable to the identification and removal of asbestos-bearing materials. If the materials containing *asbestos* are in good condition, it is better to keep them than to remove them. Removal is only justified immediately when the degradation and release of the fibers of said materials is identified, and removal must be carried out by certified companies that have specialized equipment and personnel for this purpose.

The WHO (2010a) recommends that the elimination of asbestos-related diseases should take place through the following public health actions:

1. Recognizing that the most efficient way to eliminate asbestos-related diseases is to stop the use of all types of *asbestos*
2. Replacing asbestos with safer substitutes and developing economic and technological mechanisms to stimulate its replacement
3. Taking measures to prevent exposure to *asbestos* in place and during *asbestos* removal (abatement)
4. Improving early diagnosis, treatment, and social and medical rehabilitation of asbestos-related diseases and establishing registries of people with past and/or current exposures to *asbestos*

4.8.3 Berylliosis

Berylliosis is an inflammatory condition of the lungs caused by the inhalation of dust or vapors containing beryllium. Inhalation of beryllium dust and vapors may trigger an autoimmune response and, ultimately, lead to berylliosis (Sauer et al. 2002).

Beryllium (Be) is a very light metal (lighter than aluminum), six times more resistant than steel and refractory, which has important applications in industries, chemical, electronic, and aerospace, and occurs, particularly in the mineral called *beryl*, $Be_3Al_2Si_6O_{18}$.

Beryllium-containing dust and vapors may be produced during beryllium ore extraction and processing. It is interesting to note that under the same conditions of exposure, there are people who react unevenly to the inhalation of dust-containing beryllium. Exposure to Be occurs in a variety of industries, including aerospace, ceramics, dentistry, and nuclear weapons.

4.8.4 Siderosis

Siderosis is a nonfibrogenic or a "benign" intoxication caused by the inhalation of dust rich in iron (Fe) and accumulation of iron oxides in the lung tissues producing pneumoconiosis; the *siderosis* may occur, for example, as a result of occupational or occupational work such as extraction and processing of iron ores of the *itabirite* (hematite-bearing rock) or *taconite* (magnetite-bearing rock) types; electric arc welding; metallurgy of steel, iron, and alloys; and polishing of metals with iron.

Souza et al. (1998) report the clinical studies performed on a patient welder in the metallurgical industry.

Siderosis is a benign form of pneumoconiosis caused by the accumulation of iron oxide in macrophages within the lung (Chong et al. 2006).

4.8.5 Stannosis

Stannosis is a condition in which tin oxide is deposited in the pulmonary parenchyma tissue after the inhalation of dust-containing stannic oxide or tin oxide, SnO_2. Tin oxide is radiologically visible although there is no tissue reaction to its presence. Hence, it is a kind of nonfibrosing pneumoconiosis. Tin is a light and malleable white metal.

Exposure to tin occurs during the mining, extraction, and industrial processing of tin ores. Exposure to tin fumes in tin smelting works can also occur during fusion operations when it reaches the melting point temperature (Güllü et al. 2005).

Stannosis in tin mines is caused during the filling of bags (containing 70–80% of tin oxide) in order to be transported for tin smelters.

Grinding, briquette-making, smelting, and casting of tin as well as handling of tin oxide in industry can cause *stannosis*.

4.8.6 Manganism

Manganese (Mn), albeit being an essential element, is a known neurotoxin.

Manganism is a Parkinson-like disease attributed to excessive exposure to manganese-rich dust, particularly of occupationally exposed workers. *Manganism* was first identified in 1837 in five pyrolusite mill workers and has since been reported in hundreds of occupationally exposed workers (Mergler 1999; WHO 2004a, b).

4.8.7 Black Lung Disease or Coal Workers' Pneumoconiosis (CWP)

Black lung disease is the name initially given to the *pneumoconiosis* frequent in coal workers, a progressive debilitating respiratory disorder caused by the inhalation of coal dust. Later physicians gave to the black lung disease its official modern name – coal workers' pneumoconiosis (CWP) (Morgan and Seaton 1975).

Karkhanis and Joshi (2013) divide the disease into two categories:

1. Simple coal worker's pneumoconiosis (SCWP)
2. Complicated coal worker´s pneumoconiosis (CCWP) (Wade et al. 2011)

Initially, coal dust itself was seen as rather harmless, and the true cause of CWP was believed to be silicosis. The disease is caused by the inhaling particles of respirable crystalline silica, which also can be found in coal mine dust. Indeed, the symptoms of CWP overlap with those of silicosis; the two diseases can look similar on X-rays, and both fall within the constellation known as coal mine dust lung disease.

By the 1950s, scientists had shown with near certainty that CWP could be caused exclusively by excessive exposure to coal dust. Coal dust inhalation is also related to the development of chronic obstructive pulmonary disease that contributes to increased mortality among these patients.

4.8.8 Baritosis

Baritosis is caused by the inhalation of barium-rich dusts (Ba), a situation that may occur during the extraction and processing of barium ores, particularly *barite* ($BaSO_4$).

Experience shows that the lungs do not react much to the inhalation of dust rich in iron or barium. Effectively, people who have been exposed do not reveal any particular symptoms or deterioration of lung function, which is why both siderosis and baritose are considered benign pneumoconioses. Only long-term exposures cause lung function deterioration (Doig 1976; Wende 1956).

Barium (Ba) is a dense, white, alkaline earth metal that oxidizes rapidly in moist air and reacts with water. Ba^{2+} ion and Ba compounds (chloride, sulfate, and hydroxide) are toxic. However, insoluble Ba compounds, such as barium sulfate (*barite*), do not produce free Ba^{2+} and therefore are not toxic in humans (*barite* is therefore used as a contrast agent in diagnostics involving, e.g., X-rays). Barium sulfate (*barite*) is also used as an opacifying agent in certain cosmetic products.

In 2014, the FDA published a report on the health safety assessment of barium sulfatev used in cosmetics.

4.8.9 Talcosis

Talcosis is a pneumoconiosis due to *talc*, $Mg_3(Si_4O_{10})(OH)_2$. *Talc* is a mineral widely used in various industries such as ceramics, paper, plastics, rubber, paints, construction, and cosmetics.

Four distinct pneumoconioses (lung diseases associated with the involuntary inhalation of powder of certain minerals) attributed to the *talc* are recognized.

Three pneumoconioses are due to:

1. *Inhalation* of fine particles of pure or near-pure *talc* (*talcosis*).
2. *Inhalation* of fine particles of *talc* associated with crystalline silica (*talcosilicosis*).
3. *Inhalation* of fine particles of *talc* associated with asbestos (*talcoasbestosis*). The fourth pneumoconiosis is caused by exposure to *talc* intravenously.

Inhalation may occur during mining; mineral treatment (spraying); handicraft work using the so-called soapstone which, as a rule, in addition to talc, contains *quartz* and *asbestos*; and industrial processing work (in the above-mentioned industries). Intravenous *talc* poisoning occurs in patients who are dependent on narcotics or drugs. Illegal street drugs commonly contain adulterants and excipients such as talc, starch, and cellulose to increase their mass and which are microscopic and insoluble in size. Heroin, cocaine, and methadone are the most injected drugs. The drug tablets are crushed, mixed with water, heated, and then injected intravenously. The injected product resulting from the dissolution of tablets in addition to the active ingredient (e.g., methadone) as a rule contains *talc* as excipient. Some scientific articles on exposure to *talc* with health effects produced by the following authors are mentioned: Vallyathan and Craighead (1981), Souza et al. (2003), Bezerra et al. (2004), Marchiori et al. (2010), Griffithi et al. (2012), Siddiqui et al. (2013), Neves et al. (2016), and Escussiato et al. (2017).

4.9 Negative Health Effects of Airborne Minerals *Latu Sensu* in Natural and Anthropogenic Dusts, Gases, Ashes, and Smokes

4.9.1 Background

Some of what is reported in this subchapter is extracted from the book entitled "Minerals and Human Health: Benefits and Risks" by Gomes and Silva (2007), information that naturally is updated.

Humans can survive a few weeks without eating and several days without drinking; however, without breathing, they survive but for a few minutes. In average, daily requirements for each person are 0.5 kg food, 1.5 kg water, and 15 kg air.

According to the WHO Regional Office for Europe (2000), the daily requirement for air is estimated at 10–20 m^3. "Various chemicals are emitted into the air from both natural and man-made (anthropogenic) sources, in quantities that may range from hundreds to millions of tons annually.

Natural air pollution stems from various biotic and abiotic sources, such as plants, forest fires, volcanoes and other geothermal sources, and emissions from land and water.

Anthropogenic air pollution has existed at least since people learned to use fire, but it has increased rapidly since industrialization began, particularly with the use of fossil energy sources."

Air is a public asset as everyone needs it to breathe. Recognizing the need of humans for clean air, in 1987, the WHO Regional Office for Europe published the "Air Quality Guidelines for Europe" containing the health risk assessments of 28 chemical air contaminants, number that was changed to 35 pollutants in 2000. Also, the European Environment Agency (EEA) in 2018 issued a report entitled "Air Quality in Europe" that pretends to be an updated review of the air quality in Europe from 2000 to 2016, enhancing the progress made to meet the air quality standards established in the two EU Ambient Air Quality Directives and toward the WHO Air Quality Guidelines (AQGs).

The EEA report also presents the latest findings and estimates on population and ecosystem exposure to the air pollutants with the greatest impacts and effects.

> For example, regarding particulate matter, concentrations of particulate matter (PM) continued to exceed the EU limit values and the WHO AQGs in large parts of Europe in 2016. For PM with diameter of 10 µm or less (PM_{10}), concentrations above the EU daily limit value

> were registered in 19% of the reporting stations in 19 of the 28 EU member states (EU-28) and in 8 other reporting countries; for PM2.5, concentrations above the annual limit value were registered at 5% of the reporting stations in 4 member states and 4 other reporting countries.

Regarding toxic metals, the report states that the concentrations of arsenic (As), cadmium (Cd), lead (Pb), and nickel (Ni) in the air are generally low in Europe with few exceedances of the environmental target standards (6 ng/m^3 for As, 5 ng/m^3 for Cd, 0.5 g/m^3 for Pb, and 20 ng/m^3 for Ni), typically related to specific industrial plants.

Also, regarding the impacts of air pollution on the health of the European population, they are significant in urban areas, cutting lives short (around 400,000 premature deaths per year), increasing disease and medical costs, and reducing productivity through working days lost across the economy. Heart disease and stroke being the most common causes of premature death are attributable to air pollution, followed by lung diseases and lung cancer.

Europe's most serious pollutants in terms of harm to human health are PM, NO_2 (this widely exceeded across Europe, despite the decline of its concentration), and ground-level O_3 (despite the decline of its concentration by about 40% within the studied period). International efforts to deal with air pollution effectively just began in 1972 and continue with limited success. For the WHO (World Health Organization), polluted air is the world's largest environmental health risk. According to the WHO, in 2012, 7 million premature deaths resulted from air pollution exposure.

Urban air pollution is now emerging as one of the world's leading environmental problems. The smog associated with rapid industrialization, particularly in cities from China and India, such as Beijing, Delhi, Mumbai, and Karachi, is really terrible attaining levels ten times higher than the WHO recommended level.

Within inorganic air pollutants, arsenic, asbestos, cadmium, fluoride, hydrogen sulfide, lead, manganese, mercury, nickel, platinum, vanadium, sulfur dioxide, and particulate matter were contemplated in those guidelines.

Air is composed of a stable composition of gases, but their proportions change as we breathe. The proportion of oxygen is lower, and the carbon dioxide is higher in the air that we exhale than in the air we inhale. When we inhale, we breathe in about 21.5% of oxygen, 78% of nitrogen, and 0.3% of carbon dioxide. However, when we breathe out, we exhale approximately 17% of oxygen, 78% of nitrogen, and 4% of carbon dioxide. Also, when we inhale, air goes through our larynx, trachea, and into a network of tubes known as the bronchus and bronchioles, and then into the millions of tiny air bags or chambers in our lungs known as the alveoli. From the alveoli, the oxygen passes into the bloodstream where it is oxygenated. Oxygenated blood is pumped by the heart and is then transported to the body tissue cells, where oxygen breaks food to produce energy. During the process, carbon dioxide is produced as waste and is carried back to the lungs where it is exhaled. The body needs oxygen to metabolize food and turn it into energy.

Epidemiologists from Harvard, USA, for example, defend that many diseases are associated to the bad quality of the air we breathe. In the most important cities of the

USA and of some other countries, pollution restrictions have improved the air quality outside houses. However, inside the houses, the air quality is not satisfactory too. Tobacco smoke, gases (carbon monoxide, nitrogen monoxide, and other gases produced by computers, photocopying machines, and printers, as well as gases from glues and paints) contribute to indoor polluted air. Stephens et al. (2002) report interesting data referring to the mineralogy of cigarettes and the implications for smoking-related diseases.

Mineral dusts have impacts on climate and ecosystems as well as on human health, in the last case especially caused by particles in the nanometer size range where properties may differ significantly from those of larger particles. Millions of airborne particles enter the human respiratory system with each breath we take. Once inhaled, coarse particles may be deposited on the surfaces of the conducting airways of the upper respiratory system, whereas fine particles (generally defined as those with a diameter of <2.5 μm and known as $PM_{2.5}$) can migrate to the deepest parts of the lung where the gas exchange takes place (Plumlee et al. 2006). Ultrafine particles (<0.1 μm), the so-called nanoparticles, may even penetrate through the cell tissue that lines the lung and then transfer to other parts of the body. The inhaled particles can interact with the lung fluid or with various types of cells present in the lungs. These interactions may have adverse health effects, both acute and chronic.

Epidemiological and toxicological studies have shown that exposure to PM2.5 is linked to increases in mortality and hospital admissions due to respiratory and cardiovascular diseases (Englert 2006). We do not realize how many nanoparticles (defined as having diameters less than 50 nm) we do inhale every time we breathe; Buseck and Adachi (2008) estimate the inhalation of over 10^{12} nanoparticles on an average day, and the authors question their nature and identity means, where they come from, whether they are harmful to the environment and human health, and whether they influence global climate.

In urban areas nanoparticles are mainly anthropogenically produced by vehicles and industries, whereas in rural areas they mainly originate in vegetation (particularly biomass burning), soil, storms, and sea spray. Volcanoes, although sporadically, are huge producers of nanoparticles.

There are three pathways for nanoparticles intake into the human body: inhalation, ingestion, and dermal absorption. Whenever inhaled nanoparticles undergo deposition in all regions of the respiratory tract, the smaller particles will have the highest deposition efficiency. From the deposits in the alveolar region, the very small nanoparticles travel into the circulatory and lymphatic systems, potential intoxication much depending upon particle composition and reactivity (Nel et al. 2006).

Metals emitted from mining activities, as a rule, accumulate in the soils of the surrounding areas, and contaminating the soils poses a hazard to human health as the metals may be absorbed by vegetables grown on those soils, may be leached into underground water sources, or become airborne through wind-blown dust. Humans may therefore be exposed to the metals via inhalation, ingestion, and/or dermal absorption (Kumar et al. 2014).

Oosthuizen et al. (2015), at Mogale City, in South Africa, characterized by a long history of gold mining which has produced several non-rehabilitated mine dumps, determined the metals in the monitored, filtered, and measured airborne PM_{10} during approximately 3 months, and the health effects, both respiratory and neurological, were identified; the obtained results provided an indication of which metals from the group of 30 metals being analyzed may drive human health risks in the area.

In a very recent paper, Jeevanandam et al. (2018) present a review mainly dealing with the toxicity of nanomaterials, natural and synthetic, on mammalian cells and tissues, as well as the regulations implemented by different countries in order to reduce the associated risks.

There is increasing evidence, however, that coarser particles may also produce adverse effects (Brunekreef and Forsberg 2005). The adverse health effects include chronic bronchitis, exacerbation of asthma, fibrosis, and lung cancer (Fubini and Fenoglio 2007).

According to Gieré and Vaughan (2013), depending on the source, formation, and aging, airborne solid particles encompass a wide variety of natural and anthropogenic materials, including *sea salt particles*, *silicates* (such as quartz, clay minerals), *oxides* (iron and manganese oxides), *sulfates* (such as gypsum, anglesite), *carbonates* (such as calcite, dolomite), *alloys* (such as those of iron and manganese), *glass* (particularly volcanic glass), *biogenic material* (such as pollen, spores, plant fragments, algae, bacteria), and *combustion-derived carbonaceous particles* (such as soot). The characterization of such particles using the appropriate techniques is important to understand key interactions between the atmosphere and the solid Earth, its hydrosphere, and its biosphere.

The determination of whether or not a substance, inorganic or organic, poses a health risk to humans is based on clinical, epidemiological, and/or animal studies which demonstrate that exposure to a substance is associated with health effects (Kampa and Castanas 2008).

4.9.2 Natural Sources of Airborne Minerals **Latu Sensu** *and Health Hazards*

4.9.2.1 Dust from Desert Storms

Dust storms are the main source of nanoparticles (NPs) in desert and other terrestrial regions. Studies supported by satellite images revealed that dust storms in one region can be the source of migration of nano- and micro-sized minerals and anthropogenic pollutants to other regions located thousands of kilometers away from their origin. About 50% of the atmospheric aerosol particles that originate from dust storms are in the range 100–200 nm (Shi et al. 2005).

Buseck and Pósfai (1999) have extensively reviewed the consequence on the environment and climate of aerosol particles. The authors mentioned that the widespread transport of aerosols across oceans have a major effect on life, including the life forms at the bottom of the food chain. Another study of Al-Dabbous and Kumar (2014) revealed the presence of 5–1000 nm range of airborne NPs during summertime and dust events in busy roadsides of Kuwait.

The air contains fine mineral aerosol particles mostly identified as quartz, feldspar, mica, and clay minerals.

Similarly to the interaction minerals/water, the interaction minerals/atmosphere although less studied, is absolutely central to the Earth's sustainability (Buseck et al. 2000). Mineral/atmosphere interactions that take place in the lower layer of the Earth's atmosphere (the troposphere), which extends for 10–15 km above the Earth's surface, greatly affect atmosphere chemistry, climate, and human health (Hochella 2002).

Wind is the agent that removes and transports dust from rock or soil in suspension over great distances, a phenomenon particularly observable in the desert, where the rock or the soil is uncovered and exposed to wind action. Arid and subarid land covers about 30% of the Earth's land surface. Naturally, the finest mineral particle sizes typically less than 10 μm and mainly consisting of quartz, feldspar, mica, and clay minerals (fine-grained hydrous phyllosilicates) are those that can travel longer and higher.

According to Prospero (1999a, b, 2001), strong wind storms common in the Sahara desert produce dust plumes that cross the Atlantic to South and North America. Posfai and Molnar (2000) displayed an excellent NASA satellite image of a dust plume over the eastern Atlantic Ocean. It has been estimated that every year 260 million tons of mineral dust from the Sahara desert are blown up into the air; about 60 million tons fall down and are deposited on the Sahara desert; around 150 million tons fall down on the Atlantic Ocean; and the remaining dust travels to Europe and America producing red-colored rain and snow.

Aeolian dust, for example, provides one of the dominant external sources of iron (Fe) and other nutrients, such as phosphorous (P) and silicon (Si), to the surface waters of the open ocean (Jickells et al. 2005). Here the dust-derived nutrients stimulate phytoplankton growth, which, in turn, increases the uptake of CO_2 from the atmosphere through conversion into biomass (Baker and Croot 2010).

Globally, the most important dust-source areas are located in the arid regions of the lower latitudes (e.g., the Bodélé depression in Chad). In Bodélé the soil that is whitish or grayish, instead of reddish, mainly consists of diatomite, a fine-grained sedimentary rock composed of frustules, as a rule fragmented, of fresh water diatoms, microscopic algae which a few thousand years ago proliferated in the lakes of the region. Diatom frustules are made of cryptocrystalline silica (SiO_2). Other important dust sources occur at high latitudes, such as in the proglacial regions and in areas exposed through glacial retreat (Prospero et al. 2012). In Eastern Asia, mineral dust events that originate in the Gobi desert (Southern Mongolia and Northern China) during springtime give rise to the phenomenon called *Asian dust*.

The dust aerosols are carried eastward by the prevailing winds and pass over China, Korea, and Japan, and sometimes significant concentrations of dust can reach the Western USA. Although dust storms in the Gobi desert have occurred from time to time throughout history, they became a pronounced problem in the second half of the twentieth century due to intensified agricultural pressure and desertification. Areas affected by Asian dust experience decreased visibility and health problems, such as sore throat and respiratory difficulties.

Asthma and emphysema are two prominent health conditions in humans that are caused by terrestrial airborne dust particles (Sapkota et al. 2005; Ankamwar 2012). Dust NPs containing metals can damage tissues by producing reactive oxygen species (ROS) (Taylor 2002).

A case study shows that the air quality in Asia and North America is heavily disturbed during every spring season due to dust storms from the Gobi Desert (Husar et al. 2001; McKendry et al. 2001). More recently, Shi et al. (2009) also have reported that dust storms help to form Fe NPs in clouds, which creates pH fluctuations, and affects the atmospheric, mineralogical, physical, and chemical properties of the Saharan desert region.

4.9.2.2 Dust from Volcanic Eruptions

Volcanic eruption leads to the propulsion of an enormous content of aerosols and fine particles into the atmosphere with sizes within the range from micrometers to several nanometers (Guo et al. 2004).

According to Taylor (2002), a single volcanic eruption can release up to 30×10^6 tons of NPs in the form of ash into the atmosphere. The released NPs spread throughout the world and settle in the stratosphere and the troposphere which are the lowest atmospheric layers. The effect of NPs will be significant in areas of 10 km approximately from the volcano, and the particulate materials will affect human, animal, and plant activities by blocking and scattering the sunlight.

The volcanically erupted particles may possess heavy metals that are toxic to humans (Yano et al. 1990). The short-term effects of such particles include nose, throat, eye, and skin irritations and bronchial symptoms, while the long-term effects include diseases such as *podoconiosis* (Blundell et al. 1989; Corachán 1988) and the Kaposi's sarcoma (Mott et al. 2002; Montella et al. 1997).

As aforesaid volcanic eruptions are important sources not only of mineral dust emitted into the atmosphere but also of toxic gases which may cause health conditions. Finely particulate eruption of volcanic matter may be ejected and reach high altitudes and long distances from the volcanic vent.

Gieré and Vaughan (2013), in an article entitled "Minerals in the Air," report in a synthetic form the impacts on environment and on humans of the presence of minerals in the atmosphere, either of natural origin or of anthropogenic origin. In the authors opinion, it is only during super eruptions (potentially long-lasting, minimum weeks) that gigantic clouds of volcanic ash are produced and that humans become aware of the potential impacts on health of airborne minerals. A recent example of these gigantic clouds of volcanic ash was the super eruption of the Icelandic volcano Eyjafjallajokull. An old example mentioned by the authors is the devastating and asphyxiating clouds of ash produced by the Plinian eruption of Mount Vesuvius.

According to Miller and Wark (2008), the name “Plinian eruption” by definition is a large, violent, highly explosive eruption that sends a column of pyroclastic ejecta into the stratosphere, recalls Pliny the Elder, the Roman sage who died in the 79 A.D. during the eruption of Mount Vesuvius, and his nephew Pliny the Younger who wrote two letters, the first in August 79 A.D. providing insightful and widely read account of the eruption”.

Airborne ash presents problems to aviation, particularly in the case of super eruptions. The ash can block roads and airport runways, devastate agriculture fields, cause the collapse of house roofs, and discontinue telecommunications and air transport. The ash also can be a health hazard to the eyes and lungs.

Gaseous emissions release mostly H_2O vapor, CO_2, sulfur, and halogens (Cl, F) and cause significant changes to the normal low concentrations atmospheric of these gases or of their acids H_2SO_4, HCl, and HF (Robock 2000). In the past, major historic eruptions have caused famine and disease epidemic (Tanguy et al. 1998).

4.9.2.3 Ash, Dust, and Smoke from Wildfires

Potential ecological and environmental health risks are associated with wildfires that provide important and extensive physical and chemical impacts. According to Plumlee et al. (2014), the physical impacts include runoff and erosion in burned areas, with increase transport of materials via damaging debris flows, whereas chemical impacts include, for instance, losses of carbon and nutrients such as nitrogen from soils and increases in Ca, Mg, Na, K, sulfate, and chloride in soils. Increases also occur in available nitrogen and trace elements such as Fe, Mn, As, and Cr, organic contaminants and cyanide (a combustion by-product) in soils, sediments, and affected surface waters following fires. Cyanide-bearing compounds are used as corrosion inhibitors in the retardants (Calfee and Little 2003; Crouch et al. 2006).

The impacts of wildfires on air quality, particularly of fire smokes on human health, have also been studied extensively.

Residual ash is left behind in a burned area following a wildfire. Ash particles mixed with soil particles can easily be picked up by intense fire-caused updrafts and become entrained in the smoke plume from an active wildfire, and humans can breathe in these suspended ash and soil particles. There are two types of ash, black and white, as a function of the fire severity, which in turn is a function of the maximum temperatures being reached and the duration of the combustion at high temperatures.

Black ash is composed of remnant vegetation material that has only been partially combusted. It is coarser grained and is composed primarily of charcoal and remnants of plant structures. White ash results from a more complete combustion and is composed of very fine grains, with a chemical composition of Ca, Mg, K, and Na carbonates, oxides, hydroxides, sulfates, phosphates, and chlorides. It is easily wind-borne, the particles being so small that can be respired deep in to the lungs.

The mineral phases, particle morphologies, and major element chemical composition of the ash from some vegetation types have been studied (Canti 2003; LeBlond et al. 2008).

4.9.2.4 Volcanic Gases

Volcanic eruptions are important sources not only of mineral dust emitted into the atmosphere but also of toxic gases which may cause health conditions.

The most common constituents of volcanic gas are water vapor and carbon dioxide, but other gases may occur too. These include sulfur dioxide, sulfur trioxide, hydrogen sulfide, hydrogen fluoride, nitrogen dioxide, and radon.

Carbon dioxide, a colorless gas, is heavier than air, therefore if emitted in large concentrations may be asphyxiating to animal life by displaying normal air and thus depriving animals of oxygen. Breathing air with more than 3% of CO_2 can quickly lead to headaches, dizziness, increased heart rate, and difficulty breathing. Concentrations above about 15% quickly cause unconsciousness and death. CO_2 emissions also have the capacity to affect the global climate, but scientific studies indicate that the average global volcanic output is insignificant when compared to emissions from human activity.

Kling and Kusabake (1990) report that in 1986, in the Lake Nyos' crater, in the Cameroon volcanic zone, 1746 people died from asphyxia as consequence of a sudden irruption of huge quantities of CO_2. According to USGS, in an average year, volcanoes release between about 180 and 440 million tons of CO_2.

Sulfur dioxide is a colorless gas with a pungent odor that irritates the skin and the tissues and mucous membranes of the eyes and throat. SO_2 emissions can cause acid rain as well air pollution with consequent health problems. Volcanoes emit hydrogen halides (HF, HCl, HBr) which are strong toxic acids and highly soluble.

The composition of volcanic gases depends on the type of volcano and its eruptive state (active or quiescent). The most common volcanic gases in order of abundance are H_2O 30–90 mol%; CO_2 5–40 mol%; SO_2 5–50 mol%; H_2 <2 mol%; H_2S <2 mol %; and CO <0.5 mol%. Some of these gases can react in the atmosphere or volcanic plume to for aerosols (colloidal dispersions of liquid particles in a gas), the most important being HCl, HF, and H_2SO_4.

Williams-Jones and Rymer (2015) present a very interesting paper on the health hazards that can be caused by the toxicity of volcanic gases. Deaths could be easily identified during eruptive periods. However, gas-related deaths occur during the noneruptive periods. The long-term health effects of volcanic gases are still poorly understood.

Edmonds et al. (2018) named the volcanic gases as the silent killers. The effects of volcanic gases on life may be direct, such as asphyxiation, respiratory diseases, and skin burns, or indirect as is the case of regional famine caused by the cooling that results from the presence of sulfate aerosols injected into the stratosphere during explosive eruptions.

On 21 May 2018, the mass media reported that during the Kilauea eruption, in Hawaii, the toxic volcanic fumes from the "lava haze" (gas plume formed when molten rock or lava pouring into the cool seawater and boiling it) and "vog" (volcanic smog) have caused eye irritation, skin irritation, and respiratory difficulties.

Trace metals, some potentially toxic such as Pb, Cd, Zn, Cu, Hg, and Se, occur abundantly in the stable plumes of volcano degasification. Garret (2000) reports that the 1991 eruption of Mount Pinatubo, in the Philippines, ejected about 20 million tons of SO_2; 800,000 tons of Zn; 600,000 tons of Cu; 500,000 tons of Cr; 100,000 tons of Pb; 10,000 tons of As; 1000 tons of Cd; and 800 tons of Hg in only 2 days of activity. From these figures, which correspond to only one volcanic eruption, we easily realize the enormous quantities of gases and metals that are emitted every year to the Earth's surface, as well to the atmosphere and to the hydrosphere by volcanic eruptions occurring in continents or in oceans (here through the numerous vents particularly located along mid-ocean ridges).

According to USGS, the 1991 eruption of Mount Pinatubo is thought to have injected more than 250 megatons of gas into the upper atmosphere on a single day.

Volcanoes represent a potentially important natural source of mercury (Hg) in the atmosphere which has become of environmental interest, particularly on local environments, and many areas of geothermal activity have long been associated with elevated levels of mercury in soils and air, which has happened in Hawaii, Iceland, in the western parts of the USA, and New Zealand.

Worldwide emissions of mercury from volcanoes vary widely, from approximately 1 ton/year (Ferrara et al. 2000) to >800 tons/year (Varekamp and Buseck 1986). Nriagu and Becker (2003) presented a time-averaged inventory of subaerial emissions of mercury released directly to the atmosphere from a large number of volcanoes that were active during a 20-year period and found regional differences in average emissions. Very recently Vigneri et al. (2016), considering that in the last two decades thyroid cancer incidence has increased worldwide and that thyroid cancer incidence is markedly increased in volcanic areas, report epidemiological studies carried out in the volcanic area of Mount Etna, in Sicily.

Non-anthropogenic pollution with heavy metals has been documented, either in soils, water, and atmosphere. High levels of heavy metals were measured in the urine and in the scalp of individuals living in volcanic areas comparatively to individuals living in adjacent nonvolcanic areas. These studies are an important contribution to better understand thyroid biology and heavy metals role in human thyroid carcinogenesis.

4.9.3 Anthropogenic Sources of Airborne Minerals and Health Hazards

By far the greatest contributing factors to air pollution today are those that are the result of human impact, i.e., man-made sources and causes. These are largely the result of human reliance on fossil fuels and heavy industry.

The man-made sources are mostly related to the burning of multiple types of fuel and can be classified into the following types:

1. Stationary sources include smoke stacks of fossil fuel power stations (using coal), manufacturing facilities (factories), waste incinerators, and furnaces and other types of fuel-burning heating devices and metal smelters.
2. In developing and poor countries, traditional biomass (includes wood, crop waste, and dung) burning is the major source of air pollutants.
3. Mobile sources include motor vehicles, marine vessels, and aircraft.
4. Controlled burn practices in agriculture and forest management.
5. Fumes from paint, hair spray, varnish, and aerosol sprays produce volatile organic compounds.
6. Military resources, such as nuclear weapons, toxic gases, germ warfare, and rocketry.
7. Fertilized farmer land, source of nitrogen oxides.
8. Construction materials and products.

Combustion of coal and other fuels with significant ash content has the highest potential to emit particulate matter. The emission of heavy metals during combustion processes very much depends on the fuels' nature. The content of heavy metals, As, Cd, Cr, Cu, Hg, Ni, Pb, Se, Zn, and V, released from coal combustion as compounds (e.g., oxides and chlorides) could be several orders of magnitude higher than in oil. Also, the combustion of fuels used in terrestrial, aerial, and naval transportation is a source of air pollutants, heavy metals included. Biomass burning, related to forest fires and domestic wood burning, is another important source of air pollutant.

Mining operations are important sources of health effects associated with inhalation of airborne toxic substances. Martin et al. (2014) report the health effects associated with inhalation of airborne arsenic (As) arising from mining operations.

Construction workers may be exposed to a number of toxic substances, such as cement, wood dust, diesel exhaust, mineral wool, asbestos, paints and varnishes, etc. van Thienen and Spee (2008) present a good review of the health effects of construction materials and construction products. Gbadebo and Bankole (2007) have analyzed the concentration levels of potentially toxic and harmful elements contained in the airborne cement dust generated by a cement factory mill in Nigeria.

Ambient air pollutants can cause several types of health effects: eye irritation, and acute and long-term toxic effects.

Gas emissions from agriculture and animal husbandry are created by cultivation of crops and livestock. Methane is produced by cattle. Landfills also account for methane generation.

Mining and smelting activities are responsible for the extensive generation of dust particles, which can have a negative effect on various compartments of the environment, especially in dry and semi-dry areas (Castillo et al. 2013; Csavina et al. 2012). Soils are mainly influenced by the dust emissions from these operations (Ettler et al. 2011, 2012). Wind dispersion of the soil and industrial dusts can have direct effects on the population (through dust ingestion or inhalation, hand-to-mouth behaviors) (Ettler et al. 2012) or indirect effects via the food chain due to consumption of foods grown in the contaminated soils and consumption of improperly washed vegetables (Schreck et al. 2012).

Ettler et al. (2014a) have studied the smelter emissions of Cu-Co smelters in the Zambia Copperbelt and found out potential health risks related to occupational exposure to dust in and near the smelter operations and indicated the need for accurate determination of possible exposure pathways in industrial areas in developing countries where higher unintentional dust ingestion rates can be assumed compared to the EU. In a recent work, Ettler et al. (2019) studied the oral bioaccessibility of As, Cd, Cu, Pb, Sb, and Zn in bulk samples and PM10 fraction of mine tailing and smelting dusts of northern Namibia, and the authors found out that the extremely high As and Pb bioaccessibilities in the smelter dusts were caused by the presence of highly soluble phases such as arsenolite and metal arsenates, unstable under the acidic conditions of simulated gastric fluid. Also, despite rather conservative assumptions (an adult of 70 kg, a dust ingestion rate of 50 mg/day), the exposure estimates proved that As, Pb, and to a lesser extent also Cd significantly exceeded tolerable daily intake limits of these contaminants especially for the smelter dust samples. Highly bioaccessible metal(loid)s demonstrate that careful handling of these materials as well as the currently adopted safety measures (mouth filters) are necessary to reduce the smelter staff's exposure to contaminated dust.

References

Abe-Matsumoto LT, Sampaio GR, Bastos DH (2015) Suplementos vitamínicos e/ou minerais: regulamentação, consumo e implicações à saúde. Cad. Saúde Pública, Rio de Janeiro 31(7):1371–1380. https://doi.org/10.1590/0102-311X00177814

Adriano DC (2001) Trace elements in terrestrial environments: biochemistry, bioavailability and risk of metals. Springer, Berlin

Alam MGM, Allinson G, Stagnitti F, Tanaka A, Westbrooke M (2002) Arsenic contamination in Bangladesh groundwater: a major environmental and social disaster. Int J Environ Health Res 12(3)

Al-Dabbous AN, Kumar P (2014) The influence of roadside vegetation barriers on airborne nanoparticles and pedestrian exposure under varying wind conditions. Environ Sci Technol 48:13634–13643

Al-Fartusie FS, Mohssan SN (2017) Essential trace elements and their vital role in human body. Indian J Adv Chem Sci 5(3):127–136

Alina M, Azrina A, Mohd Yunus AS, Mohd Zakiuddin S, Mohd Effendi H, Muhammad RR (2012) Heavy metals (mercury, arsenic, cadmium, plumbum) in selected marine fish and shellfish along the Straits of Malacca. Int Food Res J 19(1):135–140

Altermann W, Kazmierczack J, Oren A, Wright DT (2006) Cyanobacterial calcification and its rock-building potential during 3.5 billion years of Earth History. Geobiology 4:147–166

Angeli JK, Pereira CAC, Faria TOF, Stefanon I, Padilla AS, Vassallo DV (2013) Cadmium exposure induces vascular injury due to endothelial oxidative stress: the role of local angiotensin II and COX-2. Free Rad Biol Med 65:838–848

Ankamwar B (2012) Nanotechnology's environmental impact. Bionano Frontier, Eco Revolution, Colombo, pp 207–210

Aoki T (2004) Copper defficiency and clinical practice. JMAJ 47(8):365

Araki T, Holick MF, Afonso BD, Charlap E, Romero CM, Rizk D (2011) Viamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. J Clin Endocrinol Metab 96:3603–3608

Ayoob S, Gupta AK (2006) Fluoride in drinking water: a review on the status and stress effects. Crit Rev Environ Sci Technol 36:433–487

Azbar N, Turkman A (2000) Defluoridation in drinking waters. Water Sci Technol 42:403–407

Baker AR, Croot PL (2010) Atmospheric and marine controls on aerosol ion solubility in seawater. Mar Chem 120:4–13

Banks D, Reimann C, Royset O, Skarphagen H, Saether OM (1995) Natural concentrations of major and trace elements in some Norwegian bedrock groundwaters. Appl Geochem 10:1–16

Bashir MT, Ali SB, Adris A, Haroon R (2013) Health effects associated with fluoridated water resources: a review of Central Asia. Asian J Water Environ Pollut 10:29–37

Bech J (1987) Les Terres Medicinals, Discurs per Reial Academia de Farmàcia de Barcelona, Reial Académia de Farmácia de Barcelona (ed.), CIRIT (Generalitat de Catalunya), Barcelona, 105pp

Beck MA (2001) Antioxidants and viral infections: host immune response and viral pathogenicity. J Am College Nutr 20(5):384S–388S

Becker K (1999) Is radon dangerous for our health? In: Proceedings of the 7th international conference on Nuclear engineering Special Symposium, Tokyo, Japan

Bellia JP, Birchall JD, Roberts NB (1994) Beer: a dietary source of silicon. Lancet 343:235

Belmonte L, Mansy SS (2016) Metal catalysts and the origin of life. Elements 12:413–418

Bernhoff RA (2012) Mercury toxicity and treatment: a review of the literature. J Environ Public Health:460508. https://doi.org/10.1155/2012/460508

Bezerra O, Dias EC, Carneiro A, Galvão MAM (2004) Pneumoconiose por exposição ao talco entre artesãos de pedra-sabão em Ouro Preto, Minas Gerais, Brasil. Ver Bras Med Trab, Belo Horizonte 2(3):224–234

Bibi S, Farooqi A, Hussain K, Haider N (2015) Evaluation of industrial based absorbents for simultaneous removal of arsenic and fluoride from drinking water. J Clean Prod 87:882–896

Biri A, Bozkurt N, Turp A, Kavutcu M, Himmetoglu O, Durak I (2007) Role of oxidative stress in intrauterine growth restriction. Gynecol Obstetr Investig 64(4):187–192

Bissen M, Frimmel FH (2003) Arsenic: a review. Part I: Occurrence, toxicity, speciation, mobility. Acta Hydrochimica et Hydrobiologica 31:9–18

Blundell G, Henderson WJ, Price EW (1989) Ann Trop Med Parasitol 83:381–386

Bogden JD, Oleske JM, Louria DB (1997) Lead poisoning: one approach to a problem that won't go away. Environ Health Perspect 105(12):1284–1287. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1470406/

Bolland M, Avenell A, Baron J, Grey A, MacLennan G, Gamble G, Reid I (2010) Effects of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ Res

Bolland MJ, Grey A, Avenel A, Reid IR (2015) Calcium supplements increase risk of myocardial infarction. J Bone Miner Res 30:389–390

Boni A, Pugliese C, Cláudio CC, Patin RV, Oliveira FLC (2010) Vitaminas antioxidantes e prevenção da arteriosclerose na infância. Ver Paul Pediatr 28:373–380

Bowell R, Alpers CN, Jamieson H, Nordstrom DK (2014) The environmental geochemistry of arsenic: an overview. Rev Mineral Geochem 79:1–16

Bowman CA, Bobrowsky PT, Selinus O (2003) Medical geology: new relevance in the earth sciences. Episodes J Int Geosci 26(4):270–277
Brindha K, Elango L (2011) Fuoride in groundwater: causes, implications and mitigation measures. Fuoride Prop Appl Environ Manag 1:111–136
Brochin R, Leone S, Phillips D, Shepard N, Zisa D, Angerio A (2008) The cellular effect of lead poisoning and its clinical picture. GUJHS 5(2):1–8
Brock JH (1985) Transferrins. In: Harrison PM (ed) Metalloproteins, v.2. MacMillan, London, pp 183–262
Brunekreef B, Forsberg B (2005) Epidemiological evidence of effects of coarse airborne particles on health. Eur Respir J 26:309–318
Buck BJ, Londono SC, McLaurin BT, Metcalf R, Mouri H, Selinus O, Shelembe R (2016) The emerging field of medical geology in brief: some examples. Environ Earth Sci 75:449. https://doi.org/10.1007/s12665-016-5362-6
Buseck PR, Adachi A (2008) Nanoparticles in the atmosphere. Elements 4:389–394
Buseck PR, Pósfai M (1999) Airborne minerals and related particles: effects on climate and the environment. Proc Natl Acad Sci U S A 96:3372–3379
Buseck PR, Jacob DJ, Pósfai M, Li J, Anderson JR (2000) Minerals in the air: an environmental perspective. Int Geol Rev 42:577–593
Calfee RD, Little EE (2003) Effects of a fire-retardant chemical to fathead minnows in experimental streams. Environ Sci Pollut Res 10:296–300
Canti MG (2003) Aspects of the chemical and microscopic characteristics of plant ashes found in archaeological soils. Catena 54:339–361
Carbajo JM, Maraver F (2016) Absorção cutânea de sulfureto de hidrogénio. Revista Factores de Risco da Sociedade Portuguesa de Cardiologia 41:54–62
Carbone M, Baris I, Bertino P, Brass B, Comertpay S, Dogan AU et al (2011) Erionite exposure in North Dakota and Turkish villages with mesothelioma. PNAS 108(33):13618–13623
Carlisle EM (1972) Silicon, an essential element for the chick. Science 178:619–620
Carretero MI (2002) Clay minerals and their beneficial effects upon human health: a review. Appl Clay Sci 21:155–163
Carretero MI, Gomes CSF, Tateo F (2013) Chapter 5.5: Clays, drugs and human health. In: Developments in clay science, vol 5B. Elsevier, pp 1–42
Carvalho F (2019) Radon and lung cancer: the need for national action plans. In: The 8th international conference on Medical Geology. Abstracts Book
Castillo S, de la Rosa JD, de la Campa AMS, González-Castanedo Y, Fernández-Caliani JC, Gonzalez I et al (2013) Contribution of mine wastes to atmospheric metal deposition in the surrounding area of an abandoned heavily polluted mining district (Rio Tinto mines, Spain). Sci Total Environ 449:363–372
Chakraborty S, Dutta AR, Sural S, Gupta D, Sen S (2013) Ailing bones and failing kidneys: a case of chronic cadmium toxicity. Ann Clin Biochem 50(5):492–495
Chan HM, Egeland GM (2004) Fish consumption, mercury exposure, and heart diseases. Nutr Rev 62(5):521–526
Chen D (1989) Discovery and research of lorandite in China. Acta Miner Sin 9:141–142. (abstract in English)
Chen CJ, Wu SK, Wang YB, Hou JF, Ma L, Sun XY (2012) Recent researches of synthetic mercury sulfide in traditional medicine system. Zhongguo Zhong Yao Za Zhi 37:2968–2970
Chen P, Xu R, Yan L, Wu Z, Wei Y, Zhao W, Wang X, Xie Q, Li H (2017) Properties of realgar bioleaching using an extremely acidophilic bacterium and its antitumor mechanism as an anticancer agent (2017). Biol Res 50:17. https://doi.org/10.1186/s40659-017-0122-y
Chong S, Lee K, Chung M, Han J, Kwon J, Kim T (2006) Pneumoconiosis: comparison of images and pathologic findings. RadioGraphics 26(1):59–77G
Chowdhury UK, Biswas BK, Chowdhury TR, Samanta G, Mandal BK, Basu GC, Chakraborti D (2000) Groundwater arsenic contamination in Bangladesh and West Bengal, India. Environ Health Perspect 108(5):393–397

Chwirka J, Thompson BM, Stomp JM (2000) Removing arsenic from groundwater. J Am Water Works Assoc 92:79–88

Clarkson T (2006) The toxicology of mercury and its chemical compounds. Crit Rev Toxicol 36:609–662

Combs GF (2005) Geological impacts on nutrition. In: Sellinus O, Alloway B, Centeno J, Finkelman R, Fuge R, Lindh U, Smedley P (eds) Essentials of medical geology: impacts of the natural environment on public health. Elsevier Academic Press, pp 151–177

Corachán M (1988) Endemic non-flarial elephantiasis of the lower limbs: podoconiosis. Med Clin (Barcelona) 91:97–100

Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S et al (2014) Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25(10):2359–2381. https://doi.org/10.1007/s00198-014-2794-2

Crouch RL, Timmenga HJ, Barber TR, Fuchsman PC (2006) Post-fire surface water quality: comparison of fire retardant versus wildfire-related effects. Chemosphere 62:874–889

Csavina J, Field J, Taylor MP, Gao S, Landázuli A, Betterton EA et al (2012) A review on the importance of metals and metalloids in atmospheric dust and aerosol from mining operations. Sci Total Environ 433:58–73

Dar MA, Sankar K, Dar IA (2011) Fluorine contamination in groudwater: a major challenge. Environ Monit Assess 173:955–968

Das R, Das M, Ali S, Todkar M, Dubey AK, Adwani J (2019) Role of toxic metals such as arsenic, lead, cadmium, mercury, and copper in public health and cardiovascular disease: a review. https://www.researchgate.net/publication/331562885

Di Bona KR, Love S, Rhodes NR, McAdory D, Sinha SH, Kern N, Kent J, Strickland J, Wilson A, Beaird J, Ramage J, Rasco JF, Vincent JB (2011) Chromium is not an essential trace element for mammals: effects of a "low-chromium" diet. J Biol Inorg Chem 16(3):381–390. https://doi.org/10.1007/s00775-010-0734-y

Dietary guidelines for Americans (2010) 7th edition USA Government Printing Office, Washington, DC

Dietary reference intakes: recommended dietary allowances and adequate intakes for vitamins and elements. http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables

Dissanayake CB (1991) The fluoride problem in the groundwater of Sri-Lanka environmental management and health. Int J Environ Stud 38:137–156

Dissnayake CB, Chandrajith R (2006) Inorganic aspects of medical geology. Z. dt. Ges. Geowiss. 157/3, 327–335, 5 figs., 1 tab., Stuttgart

Doig AT (1976) Baritosis: a benign pneumoconiosis. Thorax 31:30–33

Dong H (2012) Clay-microbe interactions and implications for environmental mitigation. Elements 8:113–118

Dong H, Lu A (2012) Mineral-microbe interactions and implications for remediation. Elements 8:95–100

Dunn CE, Irvine DG (1993) Relevance of a litho-geochemical database to epidemiological studies in Central Saskatchewan, Canada. Appl Geochem 2:215–222

Edmonds M, Grattan J, Michnowicz S (2018) Volcanic gases: silent killers. Adv Volcanol:65–83

Edmunds WM, Smedley PL (2005) Fluoride in natural waters. In: Selinus O (ed) Essentials of medical geology. Elsevier Academic Press, pp 301–329

Edmunds WM, Smedley PL (2013) Fuoride in natural waters. Essentials of medical geology. Springer, Berlin, pp 311–336

EEA (European Environment Agency) (2018) Air quality in Europe-2018 report, 83pp. ISBN:978-92-9213-989-6. https://doi.org/10.2800/777411

El-Rahman SS (2003) Neuropathology of aluminum toxicity in rats (glutamate and GABA impairment). Pharmacol Res 47(3):189–194

Englert N (2006) Fine particles and human health: a review of epidemiological studies. Toxicol Lett 149:235–242

EPA (Environment Protection Agency, Washington, DC) (2005a) Toxicological review of barium and compounds. March 1998, minor revisions Jan 1999. Reference dose revised Jun 2005, EPA/635/R-05/001. www.epa.gov/iris

EPA (Environment Protection Agency, Washington, DC) (2005b) A citizen's guide to radon- The guide to protecting yourself and your family from radon. US EPA 402-K02-006. http://www.epa.gov/radon/pubs/citguide-html

Erickson BE (2007) The therapeutic use of radon: a biomedical treatment in Europe, an "alternative" remedy in the United States. Dose-Response 5(1):48–62

Escussiato DL, Gomes Ferreira R, Adriano de Barros J, Marchiori E (2017) Talcose pulmonar causada por injeção intravenosa de metadona. J Bras Pneumol 43(2):154–155

Ettler V, Mihaljević M, Křıbek B, Majer V, Šebek O (2011) Tracing the spatial distribution and mobility of metal/metalloid contaminants in Oxisols in the vicinity of the Nkana copper smelter, Copperbelt province, Zambia. Geoderma 164:73–84

Ettler V, Křıbek B, Majer V, Knésl I, Mihaljević M (2012) Differences in the bioaccessibility of metals/metalloids in soils from mining and smelting areas (Copperbelt, Zambia). J Geochem Explor 113:68–75

Ettler V, Konecný L, Kovářová L, Mihaljević M, Šebek O et al (2014a) Surprisingly contrasting metal distribution and fractionation patterns in copper smelter affected tropical soils in forested and grassland areas (Mufulira, Zambian Copperbelt). Sci Total Environ 473–474:117–124

Ettler V, Vıtková M, Mihaljević M, Šebek O, Klementová M et al (2014b) Dust from Zambian smelters: mineralogy and contaminant bioaccessibility. Environ Geochem Health. https://doi.org/10.1007/s10653-014-9609-4

Ettler V, Cihlovaa M, Jarošikovaa A, Mihaljeviča M, Drahotaa P, Křibekb B, Vaněkc A, Penižekc V, Sracekd O, Klementovae M, Engelf Z, Kamonag F et al (2019) Oral bioaccessibility of metal(loid)s in dust materials from mining areas of northern Namibia. Environ Int 124:205–215

Fairweather-Tait SJ, Cashman K (2015) Minerals and trace elements. In: Bier D et al (eds) Nutrition for the primary care provider, vol 111. World Rev Nutr Diet, Basel, Karger, pp 45–52

Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE et al (2011) selenium in human health and disease. Antioxid Redox Signal 14(7):1337–1383

Falkenback A, Kovacs J, Franke A, Jorgens K, Ammer K (2005) Radon therapy for the treatment of rheumatic diseases: review and meta-analysis of controlled clinical trials. Rheumatol Int 25:205–210

Farooq MA, Dietz K-J (2015) Silicon as versatile player in plant and human biology: overlooked and poorly understood. Front Plant Sci 6:Article 994. https://doi.org/10.3389/fpls.2015.00994

Fawell J, Bailey K, Chilton J, Dahi E, Fewtrell L, Magara Y (2006) Fluoride in drinking water. World Health Organization (WHO), IWA Publishing, pp 97–London, 117

Fazal MA, Kawachi T, Ichion E (2001) Extent and severity of groundwater arsenic contamination in Bangladesh. J Water Int 26(3):370–379

FDA (Food and Drug Administration, Washington DC) (2014) Safety assessment of barium sulfate as used in cosmetics, 9pp

Ferguson JF, Gavis J (1972) A review of the arsenic cycle in natural water. Water Res 6:1259–1274

Fergusson JE (1990) The heavy elements: chemistry, environmental impact and health effects. Pergamon Press, Oxford, 614p

Ferrara R, Mazzolai B, Lanzillotta E, Nucaro E, Pirrone N (2000) Volcanoes as emission sources of atmospheric mercury in the Mediterranea basin. Sci Total Environ 259:115–121

Fiolhais C, Marçal D (2017) A Ciência e os seus Inimigos. Gradiva Publicações, S.A. (editor), 282pp. ISBN:978-989-616-799-8

Flick DF, Kraybill HF, Dimitroff JM (1971) Toxic effects of cadmium: a review. Environ Res 4(2):71–85

Fordyce F (2005) Chapter 15: Selenium deficiency and toxicity in the environment. In: Selinus O, Alloway BJ, Centeno J, Finkelman RB, Fuge R, Lindh U, Smedley P (eds) Essentials of medical geology: Impacts of the natural environment on public health. Elsevier, Academic Press, pp 373–416

Fubini B, Fenoglio I (2007) Toxic potential of mineral dusts. Elements 3:407–414

Fukuda H, Ebara M, Yamada H, Arimoto M, Okabe S, Obu M, Yoshikawa M, Sugiura N, Saisho H (2004) Trace elements and cancer. JMAJ 47(8):391–395

Gaby AR (2011) Nutritional medicine. Fritz Perlberg Publishing, Concord

Garret RG (2000) Natural sources of metals in the environment. Hum Ecol Risk Assess 6(6):954–963

Gbadebo AM, Bankole OD (2007) Analysis of potentially toxic metals in airborne cement dust around Sagamu, Southwestern Nigeria. J Appl Scie 7:35–40. https://doi.org/10.3923/jas.2007.35.40

Genchi G, Simicropi MS, Carocci A, Lauria G, Catalano A (2017) Mercury exposure and heart diseases. Int J Environ Res Public Health 14(1):74

Gerhardsson L, Dahlin L, Knebel R, Schutz A (2002) Blood lead concentration after a shotgun accident. Environ Health Perspect 110(1):115–117

Gieré R, Vaughan DJ (2013) Minerals in the air. Miner Matter Elem:410–411

Goc A (2006) Biological activity of vanadium compounds. Versita Central Eur J Biol 1(3):314–332

Goldschmidt VM (1954) Geochemistry. Oxford University Press, Oxford, 730pp

Gomes CSF, Silva JBP (2001) Beach sand and bentonite from Porto Santo Island: Potentialities for applications in Geomedicine/Areia de praia e bentonite da ilha do Porto Santo: Potencialidades para aplicações em Geomedicina. Madeira Rochas-Divulgações Científicas e Culturais (editor), Funchal, RAM, 60pp

Gomes CSF, Silva JBP (2007) Minerals and clay minerals. Appl. Clay Sci 36:4–421

Gomes CSF, Silva JBP (2012) Ilha do Porto Santo: Estância Singular de Saúde Natural/Porto Santo Island: Unique Natural Health Resort. Madeira Rochas – Divulgações Científicas e Culturais (editor), Funchal, RAM, 239pp. ISBN:978-972-99004-4-0

Goyer R, Golub M, Choudhury H, Hughes M, Kenyon E, Stifelman M (2004) Issue paper on the human health effects of metals. U.S. Environmental Protection Agency, Risk Assessment Forum, 1200 Pennsylvania Av, NW, Washington, DC, 20460

Grant WB, Lahore H, McDonnell SL, Carole A, Baggerly CA, French CB, Aliano JL, Bhattoa HP (2020) Evidence that Vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12(4):988. https://doi.org/10.3390/nu12040988

Grey A, Bolland M (2015) Web of industry, advocacy and academia in the management of osteoporosis. BMJ 351:h3170

Griffithi CC, Raval JS, Nichols L (2012) Intravascular talcosis due to intravenous drug use is an underrecognized cause of pulmonary hypertension. Pulm Med. https://doi.org/10.1155/2012/617531

Gröber U, Schmidt J, Kisters K (2015) Magnesium in prevention and therapy. Nutrients 7(9):8199–8226. https://doi.org/10.3390/nu7095388

Guallar E, Stranges S, Mulrow C, Appel LJ, Miller ER (2013) Annals of. Int Med 159(12):850–851

Güllü E, Karnak D, Kayacan O, Beder S (2005) A tinner with stannosis and tuberculosis. Case Rep Clin Pract Rev 6:73–76

Guo S, Bluth GJS, Rose WI, Watson IM (2004) Re-evaluation of SO2 release of the 15 June 1991 Pinatubo eruption using ultraviolet and infrared satellite sensors. Geochem Geophys Geosyst 5:Q04001

Guyonnet GS, Andrieu S, Vellas BJ (2007) The potential influence of sílica presente in drinking water on Alzheimer's disease and associated disorders. J Nutr Health Aging 11(2):119–124

Handbook of Nutritionally Essential Mineral Elements (1997) O' Dell BL, Sunde RA (eds). Marcel Dekkery Inc., New York

Hannigan R (2007) Chapter 1: What goes around comes around. Today's environmental geochemistry. In: Sarkar D, Datta R, Hannigan R (eds) Concepts and applications in environmental geochemistry, Developments in environmental science, vol 5, 1st edn. Elsevier Ltd, pp 1–8

Hazen R (2009) Genesis: rocks, minerals and the geochemical origin of life. Elem Int Mag Miner Geochem Petrol 1:135–137

Hem JD (1985) Study and interpretation of the chemical characteristics of natural water. US Geological Survey Water-Supply Paper 2254:363

Henson PJ, Chedresse MC (2004) Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. Exp Biol Med (Maywood) 229:383–392

Hochella MF (2002) Sustaining Earth: thoughts on the present and future roles of mineralogy in environmental science. Miner Mag 66(5):627–652

Hollabaugh CL (2007) Chapter 2: Modification of Goldschmidt's geochemical classification of the elements to include arsenic, mercury, and lead as biophile elements. In: Sarkar D, Datta R, Hannigan R (eds) Concepts and applications in environmental geochemistry, Developments in environmental science, vol 5, 1st edn. Elsevier Ltd, pp 9–32

Hong S, Candelone JP, Patterson CC, Boutron CF (1994) History of ancient copper smelting pollution during Roman and Medieval times recorded in Greenland ice. Science 272:246–248

Hoque MA, Burgess WG, Shamsudduha M, Ahmed KM (2011) Delineating low-arsenic groundwater environments in the Bengal Aquifer system, Bangladesh. Appl Geochem 26(4):614–623

Huang HB, Wang QZ, Wang XW, Feng X, Sun H, Li WY, Wang M (2013) Overview of current researches on Tibetan medicine "zuotai". Zhongguo Zhong Yao Za Zhi 38:2886–2888

Huang Y, Wang M, Mao X, Qian Y, Chen T, Zhang Y (2015) Concentrations of inorganic arsenic in milled rice from China and associated dietary exposure assessment. J Agric Food Chem 63:10838–10845

Husar RB, Tratt DM, Schichtel BA, Falke SR, Li F, Jaffe D, Gassó S, Gill T, Laulainen NS et al (2001) Asian dust events in April 1998. J Geophys Res Atmos 106:18317–18330

IAEA (1994) Application of hair as an indicator for trace element exposure in man. ICH. https://inis.iaea.org/collection/NCLCollectionStore/_Public/26/032/26032943.pdf?r=1&r=1

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2012) Arsenic, metals, fibers, and dust. IARC Monogr Eval Carcinog Risks Hum 100:11–465

Iitaka M (2004) Iodine deficiency disorder and clinical practice. JMAJ 47(8):371–375

Institute of Medicine Committee to Review Distary reference Intakes for Vitamin D, calcium. The National Academies Collection: reports funded by National Institutes of Health (2011) In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB (eds) Dietary reference intakes for calcium and vitamin D. National Academies Press (US), National Academy of Sciences Washington, DC.

Iqbal J, Kim HJ, Yang JS, Baek K, Yang JW (2001) Removal of arsenic from groundwater by micellar-enhanced ultrafiltration. Chemosphere 66:970–976

Ishahara Y (2001) *In vitro* studies on biological effects of fibrous minerals. Ind Health 39:94–105

Itokawa Y (2004) Deficiencies of trace elements among the aged and clinical aspects. JMAJ 47(8):382–386

IWMI (2005) Report of LDD-IWMI land zoning and Cd risk assessment activities undertaken in Phatat Pha Daeng and Mae Tao Mai sub-districts, Mae Sot, Tak Province, Thailand. International Water Management Institute, Bangkok

Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowa KN (2014) Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol 7(2):60–72. https://doi.org/10.2478/intox-2014-0009

Järup (2003) Hazards of heavy metal contamination. Br Med Bull 68(1):167–182

Jarup L, Akesson A (2009) Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238(3):201–208

Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK (2018) Review of nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol 9:1050–1074

Jickells TD et al (2005) Global iron connections between desert dust, ocean biogeochemistry, and climate. Science 308:67–71

Joshi VK, Joshi A, Dhiman KS (2017) The Ayurvedic Pharmacopoeia of India, development and perspectives. J Ethnopharmacol 197:32–38

Jugdaohsingh R (2007) Silicon and bone health. J Nutr Health Aging 11(2):99–110

Jugdaohsingh R, Anderson S, Tucker K, Elliott H, Kiel D, Thompson R, Powell J (2002) Dietary silicon intake and absorption. Am J Clin Nutr 75:887–893

Kabata-Pendias A, Pendias H (1992) Trace elements in soils and plants, 2nd edn. CRC Press, Boca Raton

Kamath SU, Pemiah B, Sekar RK, Krishnaswamy S, Sethuraman S, Krishnan UM (2012) Mercury-based traditional herbo-metallic preparations: a toxicological perspective. Arch Toxicol 86:831–838

Kampa M, Castanas E (2008) Human health effects of air pollution. Environ Pollut 151:362–367

Kan ZB (2013) An introduction of Zuotai in Tibetan patent medicine. Zhongguo Zhong Yao Za Zhi 38:1621–1623

Kanis JA, Johansson H, Oden A, Cooper C, McClooskey EV (2014) Worldwide uptake of FRAX. Arch Osteoporos 9:166. https://doi.org/10.1007/s11657-013-0166-8

Kankanamalage TN, Dharmadasa RM, Abeysinghe DC, Wijesekara RG (2014) A survey on medicinal materials used in traditional systems of medicine in Sri Lanka. J Ethnopharmacol 155(1):679–691

Kapaj S, Peterson H, Liber K, Bhattacharya (2006) Human health effects from chronic arsenic poisoning: a review. J Environ Sci Health Part A, 41 (10)

Kara C, Gunindi F, Ustyol A (2014) Vitamin D intoxication due to an erroneously manufactured dietary supplement in seven children. Pediatrics 133:240–244

Karkhanis V, Joshi JM (2012) Pneumoconioses. Indian J Chest Dis Allied Sci 55:25–34

Karkhanis VS, Joshi JM (2013) Pneumoconioses. Indian J Chest Dis Allied Sci 55:25–34

Kazantis G (2004) Mercury exposure and early effects: an overview. Medicina del Lavoro 93(3):139–147

Kazi TG, Arain MB, Baig JA, Jamali MK, Afridi HI, Jalbani N (2009) The correlation of arsenic levels in drinking water with the biological samples of skin disorders. Sci Total Environ 407:1019–1026

Kihira T (2004) Trace elements and nervous and mental diseases. JMAJ 47(8):396–401

Kling GW, Kusabake M (1990) Conclusions from Lake Nyos disaster. Nature 348:6398

Kodama H (2004) Trace element deficiency in infants and children-Clinical practice. JMAJ 47(8):376–381

Kohyama N (2005) Hazard assessment of asbestos and other fibrous minerals. Abstracts Book of the 13th international clay conference, Tokyo, 66

Konhauser KO, Lalonde SV, Planavsky NJ, Pecoits E, Lyons TW, Mojzsis S, Rouxel OJ, Barley M, Rosiere C, Fralick PW, Kump LR, Bekker A (2011) Aerobic bacterial pyrite oxidation and acid rock drainage during the Great Oxidation Event. Nature 478:369–373

Kumar B, Verma VK, Naskar AK, Sharma CS, Mukherjee DP (2014) Bioavailability of metals in soil, and health risk assessment for populations near an Indian chromite mine area. Hum Ecol Risk Assess 20:917–928

Kuwarathilaka P, Seneweera S, Ok YS, Meharg A, Bundschuh J (2019) Arsenic in cooked rice foods: assessing health risks and mitigation options. Environ Int 127:584–591

Kwon JC, Nejad ZD, Jung MC (2017) Arsenic and heavy metals in paddy soil and polished rice contaminated by mining activities in Korea. Catena 148:92–100

LeBlond JS, Williamson B, Horwell CJ, Monro AK, Kirk CA, Oppenheimer C (2008) Production of potentially hazardous respirable silica airborne particulate from the burning of sugarcane. Atmos Environ 42:5558–5568

Li S, Xiao T, Zheng B (2012) Medical geology of arsenic, selenium and thallium in China. Sci Total Environ 421–422:31–40

Lindberg DC (1992) The beginnings of Western science. University of Chicago Press, Chicago

Lindh U (2005) Biological functions of the elements. In: Selinus O, Alloway B, Centeno J, Finkelman RB, Fuge R, Lindh U, Smedley O (eds) Essentials of medical geology. Elsevier Academic Press, pp 111–116

Lindh U (2013) Biological functions of the elements. In: Selinus O, Alloway B, Centeno J, Finkelman RB, Fuge R, Lindh U, Smedley O (eds) Essentials of medical geology, Rev edn. Springer, Dordrecht, pp 129–177. https://doi.org/10.1007/978-94-007-4375-5-7

Lipski E (2012) Digestive wellness: strengthen the immune system and prevent disease through healthy digestion. McGraw-Hill, New York
Liu J (1983) Report of 4 cases of neuroretinopathy by chronic thallium poisoning. Chin J Thaumat Occup Ophtal Dis 19:22–23. (in Chinese)
Liu J, Lu Y, Wu Q, Goyer RA, Waalkes MP (2008a) Mineral arsenicals in traditional medicines: orpiment, realgar, and arsenolite. J Pharmacol Exp Ther 326(2):363–368
Liu J, Shi JZ, Yu LM, Goyer BA, Walkes MP (2008b) Mercury in traditional medicines: is cinnabar toxicologically similar to common mercurials? Exp Biol Med 233:810–817
Long J, Zhang Z (2005) Studies on environmental effect of thallium in exploring resources in southwestern area of Guizhou. Conserve Util Min Res 3:47–49
Lorentzon M, Cummings SR (2015) Osteoporosis the evolution of a diagnosis. J Intern Med 277(6):650–661. https://doi.org/10.1111/joim.12369
Maheshwari R (2006) Fluoride in drinking water and its removal. J Hazard Mater 137(1):456–463
Mandal BK, Suzuki KT (2002) Arsenic round the world: a review. Talanta 58:201–235
Marchiori E, Lourenço S, Gasparetto TD, Zanetti G, Mano CM, Nobre LF (2010) Pulmonary talcosis: imaging findings. Lung 188:165–171
Marinho A (2020) Vitamina D em tempos de pandemia. Médico News, n.° 44, Março-Abril, 6–7
Markov SA (2012) Toxic minerals.
Martin S, Griswold W (2009) Human effects of heavy metals. Environ Sci Technol Briefs Citiz 15:1–6
Martin R, Dowling K, Pearce D, Sillitoe J, Florentine S (2014) Health effects associated with inhalation of airborne arsenic arising from mining operations. Geosciences 4:128–175. https://doi.org/10.3390/geosciences4030128
McKendry IG, Hacker JP, Stull R, Sakiyama S, Mignacca D, Reid K (2001) Long-range transport of Asian dust to the Lower Fraser Valley, British Columbia, Canada. J Geophys Res Atmos 106:18361–18370
McLachlan DR, Bergeron C, Smidth JE et al (1996) Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential studies. Neurology 46(2):401–405
Meenakshi S, Viswanathan N (2007) Identification of selective ion exchange resin for fluoride sorption. J Colloid Interface Sci 308:438–450
Meharg AA, Lombi E, Williams PN, Scheckel KG, Feldmann J, Raab A, Zhu Y, Islam R (2008) Speciation and localization of arsenic in white and brown rice grains. Environ Sci Technol 42:1051–1057
Mergler D (1999) Neurotoxic effects of low-level exposure to manganese in human populations. Environ Res 80:99–102
Miller CF, Wark DA (2008) Supervolcanoes and their supereruptions. Elements 4:11–16
Ming-Ho (2005) Environmental toxicology: biological and health effects of pollutants. Chapter 12, 2nd edn. CRC Press LLC, Boca Raton. ISBN:1-56670-670-2
Montella M, Franceschi S, Geddes da Filicaia M, De Macro M, Amiani S, Balzi D, Delfino M, Lannuzzo M, Buonanno M, Satriano RA (1997) Epidiemologia e Prevenzione 21:114–117
Morais S, Garcia F, Pereira ML (2012) Chapter 10: Heavy metals and human health. In: Oosthuizen J (ed) Environmental health-emerging issues and practice. InTech, pp 227–246
Morgan WK, Seaton A (1975) Occupational lung diseases. W.B. Saunders, Philadelphia, pp 149–210
Morris C (ed) (1992) Dictionary of science and technology. Academic, San Diego
Mott JA, Meyer P, Mannino D, Redd SC (2002) Wildland forest fire smoke: health effects and intervention, evaluation, Hoopa, California. West J Med 176:157
Mou SH, Hu QT, Yan L (2007) Progress of researches on endemic selenosis in Enshi District, Hubei Province. Chin J Public Health 23(1):95–96. (in Chinese)
Mudgal V, Madaan N, Mudgal A, Singh RB, Mishra S (2010) Effect of toxic metals on human health. Open Nutraceuticals J 3:94–99

Mudhoo A, Sharma SK, Garg VK, Tseng C-H (2011) Arsenic: an overview of applications, health, and environmental concerns and removal processes. Crit Rev Environ Sci Technol 41:435–519

Muller WJ, Heath RGM, Villet MH (1998) Finding the optimum: fluoridation of potable water in South Africa. Water 24(1):21–27

National Academy of Sciences (2001) Dietary reference intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, nickel, silicon, vanadium and zinc. National Academy Press, Washington, DC

Nel A, Xia T, Mädler L, Ni N (2006) Toxic potential of materials at the nanolevel. Science 311:622–627

Neves A, Carneiro A, Bezerra O, Rocca P (2016) Talcose relacionada ao índice de exposição à poeira de pedra-sabão entre artesão de Ouro Preto, Minas Gerais, Brasil. Revista Portuguesa de Saúde Ocupacional (RPSO) 1:1–11

Ng JC, Wang J, Shraim A (2003) A global health problem caused by arsenic from natural sources. Chemosphere 52:1353–1359

Ngigi PB, Laing GD, Masinde PW, Lachat C (2020) Selenium deficiency risk in central Kenya highlands: an assessment from the soil to the body. Environ Geochem Health 42:2233–2250

Nieboer E, Sanford WE (1984) Essential, toxic and therapeutic functions of metals. In: Fleet ME (ed) MAC short course handbook, mineralogical Society of Canada, vol 10, pp 149–168

Nielsen FH, Ollerich DA (1961) Nickel a new essential trace m ineral. Fed Proc 33(6):1767–1772

Norberg GF (2009) Historical perpectives on cadmium toxicology. Toxicol Appl Pharmacol 238(3):192–200

Nriagu JO (1983) Lead exposure and lead poisoning. In: Lead poisoning in antiquity. Wiley, pp 309–424

Nriagu JO (1996) A history of global metal pollution. Science 272:223–224

Nriagu JO (1998) Tales told in lead. Science 281:1622–1623

Nriagu J, Becker C (2003) Volcanic emissions of mercury to the atmosphere: global and regional inventories. Sci Total Environ 304:3–12

Oliveira R, Santos D, Ferreira D, Coelho P, Veiga F (2006) Preparações radiofarmacêuticas e suas aplicações. Revista Brasileira de Ciências Farmacêuticas/Brazilian Journal of Pharmaceutical Sciences 42(2):151–165

Oosthuizen MA, Wright CY, Matooane M, Phala N (2015) Human health risk assessment of airborne metals to a potentially exposed community: a screening exercise. The Clear Air J 5(1):51–57

Ophaug RH, Singer L (1976) Effect of fluoride on the mobilization of skeletal magnesium and soft-tissue calcinosis during acute magnesium deficiency in the rat. J Nutr 106:771–777

Ozsvath DL (2009) Fluoride and environmental health: a review. Rev Environ Sci Biotechnol 8(1):59–79. https://doi.org/10.1007/s11157-008-9136-9

Papanikolaou NC, Hatzidaki EG, Belivanis S, Tzanakakis GN, Tsatsakis AM (2005) Lead toxicity uptate: a brief review. Med Sci Monitor 11(10):RA329

Papapoulos S, Lippuner K, Roux C, Lin CJ, Kendler DL, Lewiecki EM et al (2015) The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis; results from the FREDOM extension study. Osteoporos Int 26(12):2773–2783. https://doi.org/10.1007/s00198-015-3234-7

Parmar HS, Patel JB, Sudhakar P, Koshy V (2006) Removal of fluoride from water with powdered corn cobs. J Environ Sci Eng 48:135–138

Pauwels H, Ahmed S (2007) Fluoride in groundwater: origin and health impacts. Geosciences 5:68–73

Pershagen G, Akerblom G, Axelson O (1994) Residential radon exposure and lung cancer in Sweden. N Engl J Med 330:159–164

Plumlee GS, Morman SA, Ziegler TL (2006) The toxicological geochemistry of Earth materials: an overview of processes and the interdisciplinary methods used to understand them. Rev Mineral Geochem 64:5–57

Plumlee GS, Morman SA, Meeker GP, Hoefen TM, Hageman PL, Wolf RE (2014) Chapter 11.7: The environmental and medical geochemistry of potentially hazardous materials produced by disasters. In: Treatise on geochemistry, 2nd edn. Elsevier Ltd, pp 257–304. https://doi.org/10.1016/B978-0-08-095975-7.00907-4

Posfai M, Molnar A (2000) Aerosol particles in the troposphere: a mineralogical introduction, in EMU Notes in Mineralogy 2, Enviromental Mineralogy, chapter 10, eds. Vaughan DJ, Wogelius RA, Eotvos University Press, Budapest

Prashanth L, Kattapagari KK, Chitturi RT, Baddam VRR, Prasad LK (2015) A review on the role of essential trace elements in health and disease

Pratt S (2012) dangerous dust: Erionite – an asbestos-like mineral causing a cancer epidemic in Turkey –is found in at least 13 states. Earth Magazine, February 2012

Prospero JM (1999a) Long-transport of mineral dust in the global atmosphere: Impact of African dust on the environment of the South-Eastern United States. Proc Natl Acad Sci 96:3396–3403

Prospero JM (1999b) Long-term measurements of the transport of African mineral dust to the south-eastern United States: implications for regional air quality. J Geophys Res 104:15917–15927

Prospero JM (2001) African dust in America. Geotimes 46(1):24–27

Prospero JM, Bullard JE, Hodgkins R (2012) high-altitude dust over the north Atlantic: inputs from Icelandic proglacial dust storms. Science 335:1078–1082

Rahman IM, Begum ZA, Nakano M, Furusho Y, Maki T, Hasegawa H (2011) Selective separation of arsenic species from aqueous solutions with immobilized macrocyclic material containing solid phase extraction columns. Chemosphere 82:549–556

Rai M, Ingle AP, Medici S (eds) (2018) Biomedical applications of metals. Springer. https://doi.org/10.1007/978-3-319-74814-6-9

Rasool A, Faroqui A, Xiao T, Ali W, Noor S, Abiola O, Ali S, Nasmin W (2018) A review of global outlook on fluoride contamination in groundwater with prominence on the Pakistan current situation. Environ Geochem Health 40(4):1265–1281

Ravenscroft P, Brammer H, Richards K (2009) Arsenic in North America and Europe. Arsenic pollution: a global synthesis, RGS-IBG Book Series, pp 387–454

Robertson RHS (1996) Cadavers, choleras and clays. Mineral Soc Bull 113:3–7

Robock A (2000) Volcanic eruptions and climate. Rev Geophys 38:191–220

Rondeau V, Jacqmin-Gadda H, Commenges D et al (2001) Re: Aluminum in drinking water and cognitive decline in elderly subjects: the PAQUID cohort [letter]. Am J Epidemiol 154(3):288–290

Rondeau V, Jacqmin-Gadda H, Commenges D, Helner C, Dartiques J-F (2008) Aluminum and silica in drinking water and the risk of Alzeimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169(4):489–496. https://doi.org/10.1093/aje/kwn348

Ryan MJ, Dudash HJ, Docherty M, Geronilla KB, Baker BA, Haff GG (2010) Vitamin E and C supplementation reduces oxidative stress, improves antioxidant enzymes and positive muscle work in chronically loaded muscles of aged rats. Exp Gerentol 45:882–895

Ryan PH, Dihle M, Griffin S, Partridge C, Hilbert TJ, Tayloer R, Adjel S, Lockey JE (2011) Erionite in road gravel associated with interstitial and pleural changes: an occupational hazard in western United States. J Occup Environ Med 53(8):893–899

Sabbioni E, Ceotz L, Bignoli G (1984) Health and environmental implications of trace metals released from coal-fired power-plants: an assessment study of the situation in the European Community. Sci Total Environ 40:141–154

Saha JC, Dikshit AK, Bandyopadhyay M, Saha KC (1999) A review of arsenic poisoning and its effect on human health. Crit Rev Environ Sci Technol 29(3)

Sahai N, Kaddour H, Dalai P (2016) The transition from geochemistry to biogeochemistry. Elements 12:389–394

Samuel W, Kenneth A (2001) History of the development of arsenic derivatives in cancer therapy. Oncologist 6(suppl 2):3–10

Sancha AM (2006) Review of coagulation technology for removal of arsenic: the case of Chile. J Health Popul Nutr:254–267

Sanchez TR, Perzanowski M, Graziano JH (2016) Inorganic arsenic and respiratory health, from early life exposure to sex-specific effects: a systematic review. Environ Res 147:537–555

Sapkota A, Symons JM, Kleissl J, Wang L, Parlange MB, Ondov J, Breysse PN, Diette GB, Eggleston PA, Buckley T (2005) Impacto f the 2002 Canadian forest fires on particulate matter air quality in Baltimore Bay. J Environ Sci Technol 39:24–32

Sauer NN, McCleskey TM, Taylor TP, Neu MP, Marrone BL, Scott BL, Ehler DS, Clark NC (2002) Ligand assisted dissolution of beryllium to an understanding of chronic beryllium disease. Abstracts Book of the 18th General Meeting of the International Mineralogical Association, Edinburgh, Scotland, 180

Schoonen M, Smirnov A (2016) Staging life in an early warm "Seltzer" ocean. Elements 12:395–400

Schreck E, Foucault Y, Sarret G, Sobanska S, Cécillon L, Cestrec-Rouelle M et al (2012) Metal and metalloid foliar uptake by various plant species exposed to atmospheric industrial fallout: mechanisms involved for lead. Sci Total Environ 427–428:253–262

Schroeder MD, Balassa JJ, Tipton IH (1974) Abnormal trace metal in man-nickel. J Chron Dis 15:51–65

Schwartz K, Milne DB (1972) Growth-promoting effects of silicon in rats. Nature 239:333–334

Schweser KM, Crist BD (2017) Osteoporosis: a discussion on the past 5 years. Curr Rev Musculoskelet Med 10:265–274

Scott LJ (2014) Denosumab: a review of its use in postmenopausal women with osteoporosis. Drugs Aging 31(7):555–576. https://doi.org/10.1007/s40266-014-0191-3

Sharma SK (2003) High fluoride in groundwater cripple life in parts of India. Med Geol Newslett 7:15–16

Shenkin A (2008) Basics in clinical nutrition: physiological function and deficiency states of trace elements. E-SPEN Eur e-J Clin Nutr Metab 3:e255–e258

Shi Z, Shao L, Jones TP, Lu S (2005) Microscopy and mineralogy of airborne particles collected during severe dust storm episodes in Beijing, China. J Geophys Res Atmos 110

Shi Z, Krom MD, Bonneville S, Baker AR, Jickells TD, Benning LG (2009) Formation of iron nanoparticles and increasing iron reactivity in mineral dust during simulated cloud processing. Environ Sci Technol 43:6592–6596

Siddiqui MF, Saleem S, Badireddi S (2013) Pulmonary talcosis with intravenous drug abuse. Respir Care. https://doi.org/10.4187/respcare.02402

Silva JBP (2003) Areia de Praia da Ilha do Porto Santo: Geologia, Génese, Dinâmica e Propriedades Justificativas do seu Interesse Medicinal. Madeira Rochas- Divulgações Científicas e Culturais (editor), Funchal, RAM, 344pp

Singh R, Sharma B (2018) Chapter 9: Metal-based therapy in traditional and modern medicine systems. In: Rai M et al (eds) Biomedical applications of metals. Springer, pp 195–211

Singh R, Singh S, Parihar P, Singh VP, Prasad SM (2015) Arsenic contamination, consequences and remediation techniques: a review. Ecotoxicol Environ Saf 112:247–270

Sinha S (2014) Trace elements deficiency & cancer. IOSR J Pharm Biol Sci 9(4):21–32

Sitalakshmi R, Kumar S (2014) Trace elements in health and disease: a review. Res J Pharm Biol Chem Sci 5(5):450–455

Smedley PL, Kinniburgh DG (2002) A review of the source, behaviour and distribution of arsenic in natural waters. Appl Geochem 17:517–568

Smith IC, Carson BL (1977) Trace metals in the environment, vol 1: Thallium. Ann Arbor Science Publishers Inc, Michigan, p 307

Southam G (2012) Minerals as substrates for life: the prokaryotic view. Elements 8:101–106

Souza MB, Garcia GF, Maciel R (1998) Siderose Pulmonar. J Pneumol 24(1):51–53

Souza AS, Marchiori E, Irion KL, Ferreira A, Koch M (2003) Talcose pulmonary associada ao uso endovenoso de medicamentos orais: Relato de caso. Radiol Bras 36(3):187–190

Srivastava A, Lohani M (2015) Fluorine, a dreaded element: a review on occurrence of fluorine in environment and its standard methods of analysis. Int J Environ Res Dev 5:7–21

Steindorf K, Lubin J, Wichmann HE, Becher H (1995) Lung cancer deaths attributable to indoor radon exposure in West Germany. Int J Epidemiol 24:485–492

Stephens WE, Calder A, Herd DA, Wickenden JA (2002) Mineralogy of cigarettes: implications for smoking related lung diseases. Abstracts book of the 18th General Meeting of the international Mineralogical Association, Edinburgh, Scotland, 181

Suwatvitayakorn P, Ko M-S, Kim K-W, Chanpiwat P (2020) Human health risk assessment of cadmium exposure through rice consumption in cadmium contaminated areas of the Mae Tao sub-district, Tak, Thailand. Environ Geochem Health (2020) 42:2331–2344, doi: https://doi.org/10.1007/s10653-019-00410-7

Sverjensky DA, Lee N (2010) The great oxidation event and mineral diversification. Elements 6:31–36

Swiderski RM (2008) Quicksilver: a history of the use, lore and effects of mercury. McFarland & Company Inc Publishers, Jefferson, Noth Carolina, and London. ISBN:978-0-7864-3596-8, 310pp

Takeshi T, Goto S, Inagaki M, Okamoto Y (2009) Even very low but sustained lithium intake can prevent suicide in the general population? Med Hypothesis. https://doi.org/10.1016/j.mehy.2009.02.043. Elsevier

Taksande SR, Woecester EM (2014) Calcium supplementation in chronic kidney disease. Expert Opin Drug Saf 13:1175–1185

Tanguy JC, Ribière C, Scarth A, TJetjep WS (1998) Victims from volcanic eruptions: a revised data base. Bull Volcanol 60:137–144

Tapiero H, Townsend DM, Tew KD (2003) The antioxidant role of selenium and seleno-compounds. Biomed Pharmacother 57(3):134–144

Taylor DA (2002) Dust in the wind. Environ Health Perspect 110:A80

Taylor SR, McLennan SM (1985) The continental crust, its composition and evolution: an examination of the geochemical record preserved in sedimentary rocks. Blackwell Scientific Publishing, Oxford, p 312

Thakre D, Rayalu S, Kawade R, Meshram S, Subrt J, Labhsetwar N (2010) Magnesium incorporated bentonite clay for defluoridation of drinking water. J Hazard Mater 180:122–130

Tokuomi H, Kinoshita Y, Teramoto J, Imanishi K (1977) Hunter-Russell syndrome. Nippon Rinsho 35(1):518–519

Unger MD, Cuppari L, Titan SM, Magalhães MCT, Sassaki AL, Reis LM (2010) Vitamin D status in a sunny country: where has the sun gone? Clin Nutr 29:784–788

USEPA (United States Environmental Protection Agency) (2005a) Arsenic in drinking water fact sheet, 10.07.2011, http://www.epa.gov/safewater/arsenic.html

USEPA (United States Environmental Protection Agency) (2005b) Guidelines for carcinogen risk assessment EPA/630/P-03/001F

USEPA (United States Environmental Protection Agency) (2005c) Integrated Risk Information System (IRIS), Washington, DC. http://www.epa.gov/ncea/iris/

Vallyathan NV, Craighead JE (1981) Pulmonary pathology in workers exposed to non asbestiform talc. Human Pathol 12:28–35

van Thienen G, Spee T (2008) Health effects of construction materials and construction products. Tijdschrift voor toegepaste Arbowetenschap, TTA brochure nr 1

Varekamp JC, Buseck PR (1986) Global Hg flux frm volcanic ang geothermal sources. Appl Geochem 1:65–73

Vela-Anero A, Hermida-Gomez T, Filgueira-Fernández P, Gato-Calvo L, Burguera EF, Meijide-failde R, Blanco FJ (2018) Intra-articular administration of hydrogen sulphide ameliorates severity of experimental osteoarthritis. Osteoarthritis Cartilage 26:S287–S288

Veniale F (1997) Atti di Convegno Argille Curative. Associazione Medica Italiana di Idroclimatologia, Talassologia, e Terapia Física, Gruppo Italiano AIPEA, Salice terme/PV, 145pp

Vernadsky VI (1926) Biosphera. [The Biosphere.] Nauchnoe khimiko-technicheskoyeizdatel'stvo (Scientific Chemico-Technical Publishing), Leningrad

Vigneri R, Malandrino P, Giani F, Russo M, Vigneri P (2016) Heavy metals in the volcanic environment and thyroid cancer. Mol Cell Endocrinol 457:73–80

Viswanathan N, Meenakshi S (2009) Role of metal ion incorporation in ion exchange resin on the selectivity of fluoride. J Hazard Mater 162:920–930

Vithanage M, Bhattacharya P (2015) Fluoride in the environment: sources, distribution and defluoridation. Environ Chem Lett 13:131–147

Vitti P, Rago T, Aghini-Lombardi F et al (2001) Iodine deficiency disorders in Europe. Public Health Nutr 4:529–535

Wada O (2004) What are trace elements: their deficiency and excess states. JMAJ 47(8):351–358

Wade WA, PetsonK EL, Young B, Mogri I (2011) Severe occupactional pneumoconiosis among West Virginian coal miners: one hundred thrity-eight cases of progressive massive fibrosis compensated between 2000 and 2009. Chest 139:1458–1462

Wagner JC, McConnochie K, Gibbs AR, Pooley FD (1998) Clay minerals and health. In: Parker A, Rae JE (eds) Environmental interactions of clays. Springer, Berlin, pp 243–265

Wang L, Zhou GB, Liu P, Song JH, Liang Y, Yan XJ, Xu F, Wang BS, Mao JH, Shen ZX, Chen SJ, Chen Z (2008) Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. Proc Natl Acad Sci U S A 105:4826–4831

Wang H, Liu Z, Gou Y, Qin Y, Xu Y, Liu J, Wu JZ (2015) Apoptosis and necrosis induced by novel realgar quantum dots in human endometrial cancer cells via endoplasmic reticulum stress signaling pathway. Int J Nanomed 10:5505–5512

Ward E (2014) Addressing nutritional gaps with multivitamin and mineral supplements. Nutr J 13:72. http://www.nutritionj.com/content/13/1/72

Weiss D, Brunk DK, Goodman DA (2018) Scottsdale magnesium study: absorption, cellular uptake, and clinical effectiveness of a timed-release magnesium supplement in a standard adult clinical population. J Am College Nutr 37(4):316–327. https://doi.org/10.1080/07315724.2017.1398686

Wende E (1956) Pneumokoniose bei Baryt-und Lithoponearbeitern. Archiv fur Gewerbepathologie und Gewerbhygiene 15:171

Whitford GM (2006) Fluoride. In: Stipanuk MH (ed) Biochemical, physiological, molecular aspects of human nutrition. St. Louis, Saunders Elsevier, pp 1127–1142

WHO (1987) Air quality guidelines for Europe, Copenhagen, Denmark. WHO Regional Publications, European Series, n° 23, 2nd edn, 2000

WHO (1993) Guidelines for drinking-water quality, Geneva

WHO (1994) Fluoride and oral health. WHO Tech Rep Ser 846, Geneve

WHO (1996) Trace elements in nutrition and health. World Health Organization, Geneve. ISBN:92-4-156173-4

WHO (2002) The world health report: reducing risks, promoting healthy life, Geneve, Switzerland, 248 pp

WHO (2004a) Guidelines for drinking-water quality. Sixty-first meeting, Rome, 10–19 June 2003. Joint FAO/WHO Expert Committee on Food Additives. http://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf

WHO (2004b) Manganese in drinking water: background document for development of WHO guidelines for drinking-water quality, WHO/SDE/WSH/03.04/104. World Health Organization, Geneva

WHO (2005) Air quality guidelines for particulate matter, ozone, nitrogen dioxide -Global update

WHO (2009) Handbook on indoor radon – a public perspective

WHO (2010a) Preventing disease through healthy environments: action is needed on chemicals of major public health concern, public health and environment, World Health Organization 20 Avenue Appia, CH-1211 Geneva-27, Switzerland

WHO (2010b) Guidelines for indoor air quality-selected poluttants. Benzene, carbon monoxide, formaldehyde, nitrogen oxide, radon, naphthalene, polycyclic aromatic hydrocarbons, trichloroethylene and tetrachloroethylene

WHO (2012) Preventing disease through healthy environment: a global assessment of the burden of diseases from environmental risks, Geneva, Switzerland, 147 pp

Williams RJ (2005) Uptake of elements from a chemical point of view. In: Selinus O, Alloway B, Centeno J, Finkelman RB, Fuge R, Lindh U, Smedley O (eds) Essentials of medical geology: impacts of the natural environment on public health. Elsevier Academic Press, pp 61–85

Williams RJP, Fraústo da Silva JJR (1996) The natural selection of the chemical elements. Oxford University Press, 627pp

Williams-Jones G, Rymer H (2015) Hazards of volcanic gases. The Encyclopedia of Volcanoes, 2, pp 985–992

Wu J, Shao Y, Liu J, Chen G, Ho PC (2011) The medicinal use of realgar (As4S4) and its recent development as an anticancer agent. J Ethnopharmacol 135:595–602

Xiao TF, Boyle D, Guha J, Rouleau A, Hong YT, Zheng BS (2003) Groundwater-related thallium transfer processes and their impacts on the ecosystem: Southwest Guizhou, China. Appl Geochem 18:675–691

Xiao TF, Guha J, Boyle D, Liu CQ, Zheng BS, Wilson GC et al (2007) Potential health risk in areas of high natural concentrations of thallium and importance of urine screening. Appl Geochem 22:919–929

Yanagisawa H (2004) Zinc deficiency and the clinical practice. JMAJ 47(8):359–364

Yang GQ, Xia YM (1995) Studies on human dietary requirements and safe range of dietary intakes of selenium in China and their application to the prevention of related endemic diseases. Biomed Environ Sci 8:187–201

Yano E, Yokoyama Y, Higashi H, Nishii S, Maeda K, Koizumi A (1990) Health effects of volcanic ash: a repeat study. Arch Environ Health 45:367–337

Yin H, Kong M, Tang W (2015) Removal of fluoride from contaminated water using natural calcium-rich attapulgite as a low-cost adsorbent. Water Air Soil Pollut 226:111

Zdrojewicz Z, Strzelczyk J (2006) Radon treatment controversy. Dose-Response 4(2):106–118

Zhang QY, Mao JH, Liu P, Huang QH, Lu J, Xie YY, Weng L, Zhang Y, Chen Q, Chen SJ, Chen Z (2009) A systems biology understanding of the synergistic effects of arsenic sulfide and Imatinib in BCR/ABL-associated leukemia. Proc Natl Acad Sci U S A 106:3378–3383

Zhou DX, Liu DN (1985) Chronic thallium poisoning in a rural area of Guizhou Province, China. J Environm Health 48:14–18

Chapter 5
Metals, Life and Health

Ana Maria V. Cavaleiro and José A. S. Cavaleiro

Abstract Metal ion derivatives play biological actions of vital significance to life. Respiration, photosynthesis, drug detoxification, and cells' metabolism should be included in the group of vital functions which rule life in our planet. That led to the choice taken in this chapter for considering iron, magnesium, and cobalt as examples of the biologically active metals' group. Medicinal applications of other metal complexes are also of great impact to life; those related to cancer therapy play a key role to establish safer humans' living conditions. Due to significant developments on cancer therapy, the behavior of platinum and ruthenium complexes has been also considered in this chapter.

5.1 Metals and Vital Functions

Life on Earth depends on the simultaneous action of several agents working altogether, and minerals are a group of them. It is believed that life did start in aqueous media, probably in the sea. But whatever it took place a few billions of years ago, it is certain that some minerals always have played a key role by their participation in key life functions and luckily for living organisms they still continue to play vital functions. This is particularly certain with those appearing as minerals in the forms of free chemical elements or bonded to organic or inorganic moieties giving rise to chemical compounds.

As it is well stated, the famous periodic table highlights all chemical elements known up to now. Between all those of natural origin, we have elements which occur as bulk biological ones (such as Mg, Ca, P, N, O, S, Cl, H, Na, and K), and others (such as V, Cr, Mo, W, Mn, Fe, Co, Ni, Cu, Zn, B, Si, Se, F, and I) are essential for living species like animals, plants, and microorganisms (Williams and Fraústo da Silva 1996).

A. M. V. Cavaleiro
Department of Chemistry, Inorganic Chemistry Group, University of Aveiro, Aveiro, Portugal

J. A. S. Cavaleiro (✉)
Department of Chemistry, Organic Chemistry Group, University of Aveiro, Aveiro, Portugal
e-mail: jcavaleiro@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_5

Considering that a target of this book involves minerals and their contribution to the existing life in good health condition, a few elements will be chosen and for such choice it will be considered a few of them which play key vital functions in nature (Fe, Mg, and Co) and also other ones (Pt, Ru) which are under study as oncologic therapeutic agents.

There are two vital functions to our everyday life which are the animals' respiration and the plants' photosynthesis. How would be life if such biological functions would not be taking place? Certainly, such hypothetical life would be completely different from the one we really have. Then our life on Earth depends on the action of several chemical elements.

In the particular case of Fe and Mg vital functions, the former metal ion is involved in the respiration and drug detoxification and the latter metal one acts at the photosynthetic process. In the case of cobalt derivatives, Co(III) coenzymes related with the vitamin B_{12} vitamers play an important biological action.

Other metal complexes are being targets in studies related with the search of metal applications, and several examples can be found in the medicinal field. Particularly in studies concerned with cancer therapy, certain complexes of platinum and ruthenium have demonstrated promising properties. Some of the results already known will be considered here.

5.1.1 Iron

Iron is present in the Earth's crust as a component of *hematite*, pyrite, magnetite, chromite, siderite, goethite, and chalcopyrite. It is a transition element; its most common oxidation states are the +2 and +3 states, and depending on the ligands surrounding the metal, the Fe(II) compounds might be easily oxidized to the Fe(III) ones. And the involvement of certain iron complexes, as intermediates in several biological transformations, also requires the presence of higher oxidation states for the iron complex (Milgrom 1997).

As already stated, iron species take part in respiration, but iron complexes are also acting in several other vital functions; these are related with drug detoxification of xenobiotic processes which take place under the action of cytochromes P_{450} and other defensive actions involving certain enzymes (e.g., catalases, peroxidases).

5.1.1.1 Hemoproteins and Respiration

Animals' respiration is taking place by the action of two hemoproteins, myoglobin and hemoglobin. These hemoproteins contain 80% of the iron in human bodies; they are globular proteins containing Fe(II) complexes. Their prosthetic groups are iron complexes of protoporphyrin IX (Fig. 5.1). Iron ion is then located at the center of the porphyrin macrocycle, being coordinated to the four nitrogen atoms of the pyrrolic groups of each porphyrin macrocycle.

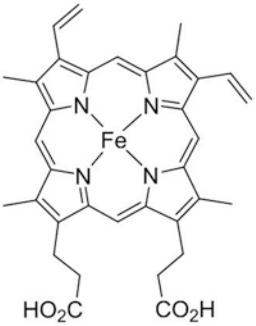


Fig. 5.1 Iron(II) protoporphyrin IX

The structures of the two hemoproteins were established by X-ray diffraction crystallography; the 1962 Nobel Prize in Chemistry was awarded to Perutz and Kendrew for their structural protein determination studies (MF Perutz and JC Kendrew; www.nobelprize.org).

5.1.1.2 Hemoglobin

Hemoglobin transports oxygen from the lungs to the muscles and brings back the carbon dioxide for exhalation. It is a tetrameric and globular hemoprotein containing four heme and four (two α- and two β-) globin groups. Each one of the two α-globins contains 141 amino acids, and each one of the other two β-globins contains 146 amino acids.

The coordination to the iron center in the prosthetic group involves its binding to the four nitrogen atoms of the planar macrocycle and the *N*-imidazole ring of a histidine residue as the fifth ligand. The resulting species is usually known as deoxyhemoglobin. The oxygenation of the former species gives rise to the oxyhemoglobin species; it has O_2 as the sixth ligand.

5.1.1.3 Myoglobin

Myoglobin is a monomeric hemoprotein which stores O_2 in muscle tissues. It contains a globin constituted by a single polypeptide chain of 154 amino acids consisting of eight α-helices (Kendrew et al. 1958; Ordway and Garry 2004). It is a folded molecular entity having the globin coordinated with the prosthetic group iron center also via an imidazole ring of a histidine residue (Fig. 5.2).

It can be stated in a mechanistic way that O_2 binds to the Fe(II) present in heme in the presence of a nitrogenous base. The Fe(II) center in deoxyhemoglobin or in deoxymyoglobin is in a high spin state and is paramagnetic; it has a covalent radius too large to fit into the plane of the four nitrogen atoms of the porphyrin. Upon oxygenation (O_2 becoming the sixth heme ligand), the Fe center becomes diamagnetic, and a reduction in its covalent radius takes place, thus bringing the iron ion into the

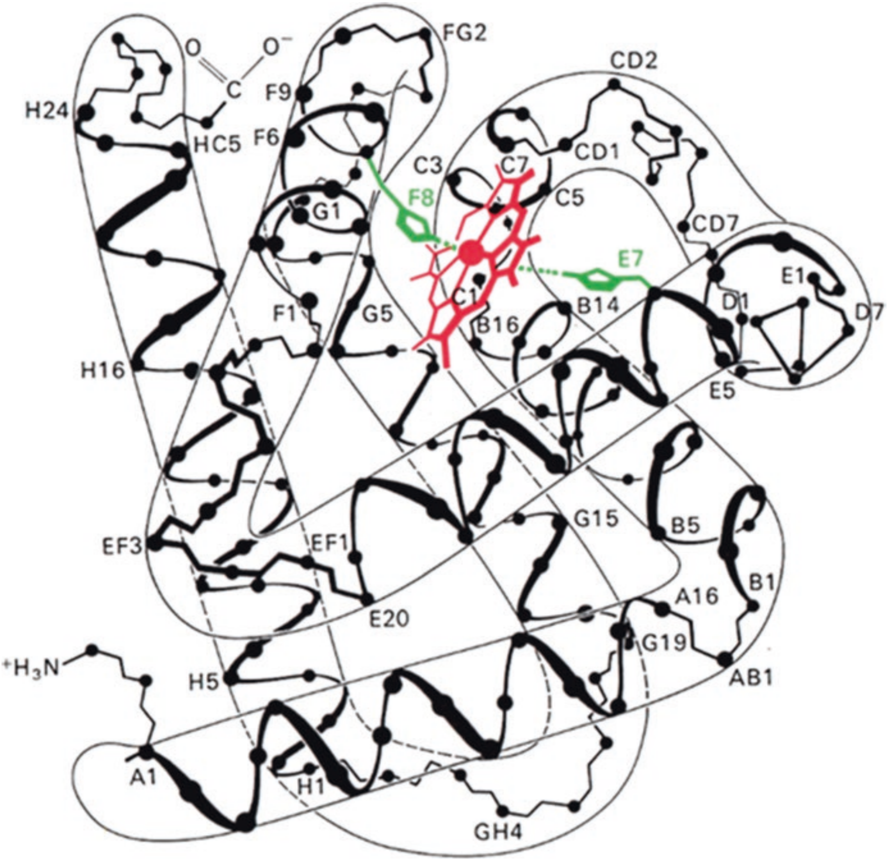


Fig. 5.2 Myoglobin model (heme group in red and α-carbons as dots) adapted from Biochemistry, Stryer L, second edition, p. 49, Freeman W. H. and Company, San Francisco, 1981

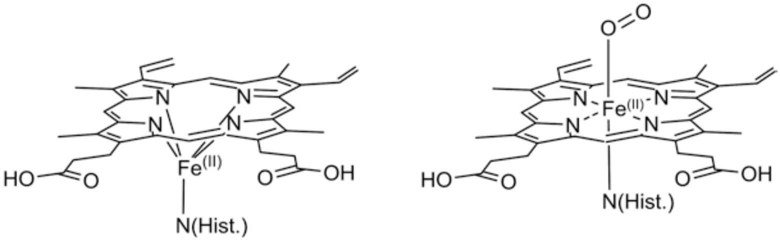


Fig. 5.3 Structures of deoxy- and oxymyoglobin derivatives

heme planar center (Fig. 5.3). A speculative suggestion related with the structure of the oxy form has been put forward by considering the species $Fe^{III}—O_2^-$ (Lippard and Berg 1994a, b).

5.1.1.4 Cytochromes P_{450} and Drug Detoxification

The first enzyme cytochrome P_{450} was isolated in 1958 from liver samples taken from rats. It can be stated that these enzymes are ubiquitous in nature occurring in species ranging from bacteria to man. These cytochromes P_{450} are a group of enzymes containing single Fe(III) protoporphyrin IX as prosthetic groups, which also contain thiolate sulfur atoms from cysteine amino acids as the fifth axial ligands. Position six is free or occupied by a water molecule (Lippard and Berg 1994a, b; Sheldon 1994; Denisov and Sligar 2010).

The iron acts as a redox center in the catalytic cycle, accepting two electrons and forming a peroxo intermediate which gives rise to a Fe(IV) oxoporphyrin radical cation; such species is the active oxidant which transfers the oxygen to an amazing variety of organic substrates (Fig. 5.4).

It has to be highlighted that such enzymes act in significant functions, particularly in metabolic events and detoxification of harmful compounds. These P_{450} enzymes are really anti-xenobiotic agents.

Chemists with research targets in catalysis and on the transformation of cheap substrates into value-added products have developed methodologies to mimic the cytochromes' action (Silva et al. 2014; Simões et al. 2013).

Iron is then a vital element in the mankind's current life since it participates in many biological processes. However, the iron concentration in living tissues has to be highly regulated within the homeostasis range of living tissues. Its deficiency in human beings brings anemic situations which require adequate treatments. And its excess can bring tissue damages due to the formation of several toxic ionic or radical reactive oxygen species (Lieu et al. 2001).

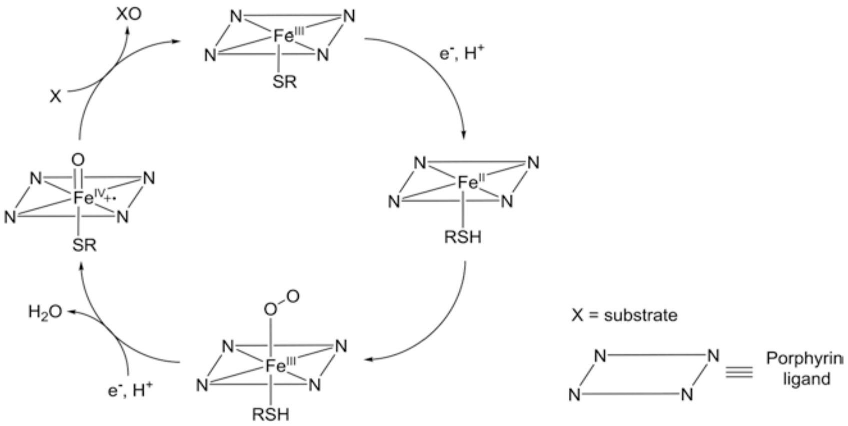


Fig. 5.4 Possible mechanism of cytochrome P_{450} oxidation of xenobiotics

5.1.1.5 Catalase and Peroxidase Enzymes

The use of molecular oxygen in vivo for biological requirements generates several oxygen reactive species which are toxic to the living organisms which require the presence of defensive means against that. Hydrogen peroxide (H_2O_2) is one of such toxic species. The action against H_2O_2 usually takes place by existing enzymes which act by destroying or using hydrogen peroxide. Such defensive enzymes contain porphyrin iron(III) complexes at their active sites. Catalase and peroxidase enzymes are examples of such important biological group. Catalase disproportionates hydrogen peroxide giving rise in that way to O_2 and H_2O. This Fe(III) enzyme has a phenolic oxygen atom from tyrosine as a ligand, and the other axial position is free to bind the substrate. Peroxidases, such as horseradish peroxidases, use hydrogen peroxide as the oxidant of special substrates. With a histidine ligand, the active oxidant is also an oxoiron(IV) protoporphyrin IX radical cation; the oxidized substrate and water are the products of such transformations.

Overall, the action of such enzymes brings the elimination of hydrogen peroxide which could have been formed as a result of certain in vivo transformations.

5.1.2 Magnesium

Magnesium is a common metal on Earth, being the eighth element in its crust. It can be obtained in high quantities from the oceans (salt-lake brines) and in smaller quantities from minerals like magnesite, kieserite, dolomite, and brucite. Other Mg minerals include cordierite, carnallite, and diopside. Magnesium is critical to all species, especially plants (https://mineralseducationcoalition.org/elements/magnesium/).

5.1.2.1 Photosynthesis

Nature is a “beautiful machine” being deeply appreciated by humans mainly when the natural events take place in clear ways. The photosynthetic process makes possible the existing life on Earth. Solar energy being converted into chemical energy is a fantastic achievement.

Chlorophyll molecules (magnesium complexes of certain tetrapyrrolic pigments) play key action in the conversion of carbon dioxide and water into oxygen and carbohydrates with the intervention of solar energy.

The highly complex photosynthetic process transforms low-energy molecules (water and carbon dioxide) into high-energy carbohydrate ones, also generating as by-product the oxygen molecules. Such molecules make possible the existing life to mankind which is taking place since several millions of years ago.

The chlorophyll pigments (mainly chlorophylls *a* and *b*; Fig. 5.5), which absorb the light energy, are located in the chloroplasts present in plants and in certain

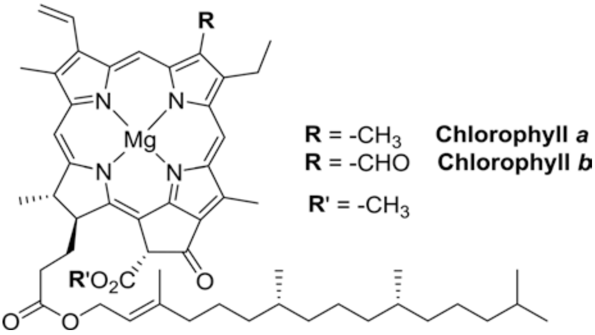


Fig. 5.5 Structures of chlorophylls *a* (R = CH_3) and *b* (R = CHO)

bacteria and green algae. The absorption features take place in the blue and red regions of the spectrum at wavelengths of 425–460 and 650–700 nm.

The presence of the Mg ion in the macrocycle gives the ring an approximate tetragonal symmetry, thus enhancing the extinction coefficient at the red region absorption. Also, the present magnesium ion has only one oxidation state, (2^+), without unwanted redox properties and also not enhancing fluorescence.

Photosynthesis is a two-step complex process involving the photochemical and non-photochemical reactions (the so-called light and dark reactions, respectively).

In the photochemical one, the chlorophyll molecules trap the light energy which allows the production of NADPH (reduced form of nicotinamide adenine dinucleotide phosphate, a reducing and electron donor agent) with the generation of ATP (adenosine triphosphate) and the oxidation of water to oxygen. Oxygen is then released into the atmosphere.

In the non-photochemical reaction, the NADPH and ATP already generated are used by enzymes to make carbohydrates by reduction of carbon dioxide. In this step, a 3-carbon unit (glyceraldehyde 3-phosphate) is initially formed. These are then used to give rise to glucose.

A simple equation related with the complex photosynthetic process in plants is the following:

$$6CO_2 + 6H_2O \xrightarrow{\text{Light}} 6O_2 + C_6H_{12}O_6$$

Human beings and other aerobic heterotrophs (like plants during non-light periods) use the formed O_2 to degrade the energy-rich carbohydrates and in that way to form CO_2 and H_2O, thus giving rise to a continuous recycling of such molecules on Earth.

5.1.3 Cobalt

Cobalt in nature appears in chemically combined form, except for small deposits found in iron meteoric alloys. The free element can be obtained by reductive smelting. Cobalt(III) metal ion is present in highly important biological compounds.

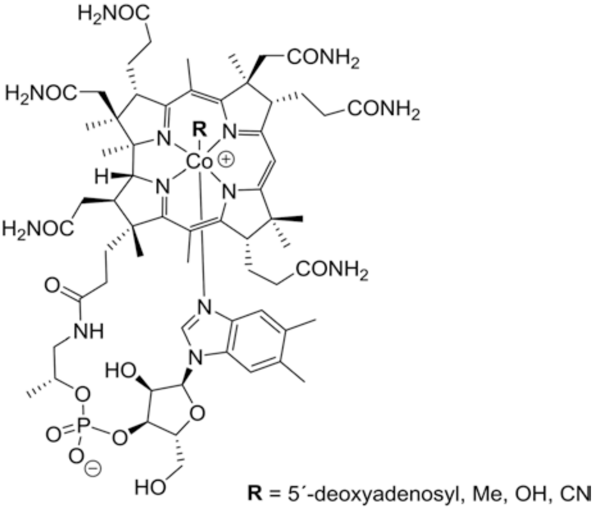


Fig. 5.6 Structure of vitamin B_{12} forms

Cobalamins are coenzymes in which cobalt(III) is the active center. Vitamin B_{12} forms (Fig. 5.6) are members of such biologically significant coenzymes.

One of the axial ligands is the 5,6-dimethylbenzimidazole group present in the associated nucleotide; the other ligand can be 5′-deoxyadenosyl, CH_3, OH, or CN, thus forming the four forms (vitamers) of B_{12}. These four compounds are also called adenosylcobalamin, methylcobalamin, hydroxocobalamin, and cyanocobalamin. The latter is usually designated by vitamin B_{12}. Its molecular structure was determined by Dorothy Hodgkin (Nobel Prize winner, 1964) using X-ray crystallography.

These compounds are biosynthesized by microorganisms (bacteria and archaea) and are stored and used by animals.

Microbial fermentation is usually the way for the corresponding production (Fang et al. 2017).

5.2 Metals and Potential Applications in Cancer Therapy

Metal-derived compounds have been used since ancient times for medicinal and agricultural purposes. In the medical side, that can be traced back for almost 5000 years (Baile et al. 2015).

Such uses along the times never brought any ideal situation. Medical improvements have been reached, but significant toxicities and unsolved problems soon became evident.

In our present times, cancer continues to be the second reason for human beings death. And so our present life is far away from any ideal situation in cancer treatment, although science has been giving a fantastic development in very good therapies.

Cancer chemotherapy currently uses several nonmetal derivatives of the big organic compounds' family. But certain metals have a landmark position still to be highlighted, improved, and approved for the success of new and better chemotherapy methodologies.

Platinum-based complexes have already demonstrated their potential application in cancer therapy, but others are currently under investigation.

Other metal complexes (e.g., Ru complexes) are selective targets in several clinical trials of chemotherapy studies.

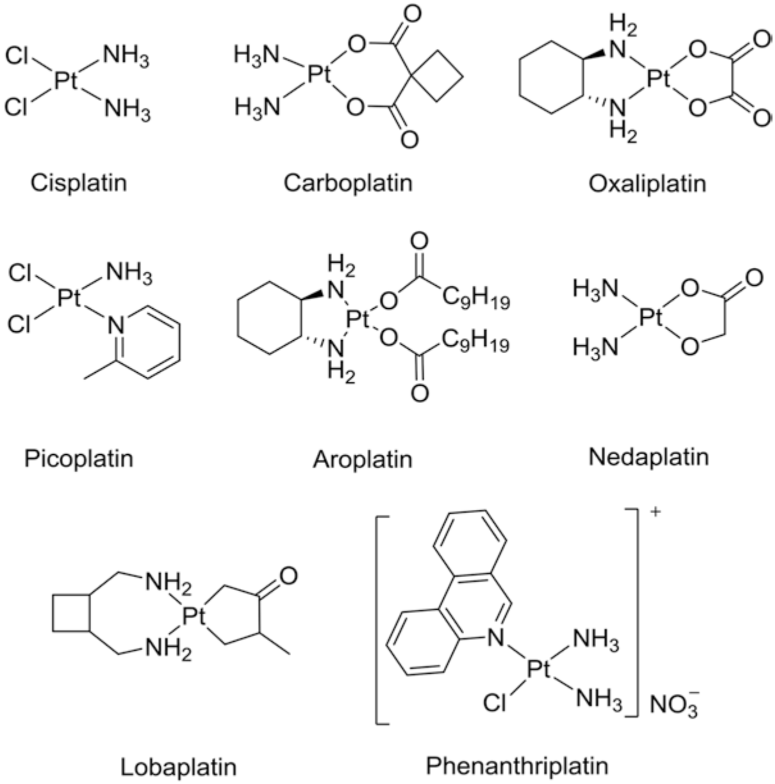


Fig. 5.7 Pt(II) complexes with anticancer properties

5.2.1 Platinum

Platinum(II) complexes application in medicine has been a research target for several decades. The discovery of the potentialities of cisplatin, *cis*-diaminedichloroplatinum(II) (Fig. 5.7), as a chemotherapeutic agent (PT1) was a landmark in the area of platinum ion metals as potential anticancer agents (Rosenberg et al. 1965). Some developed examples of platinum complexes are then shown.

In 1978, the FDA approved Platinol®, the cisplatin brand name, for the treatment of several types of cancer (bladder, ovarian, cervical, stomach, testicular, and others). Cisplatin was a promising anticancer small molecule which diffused or was biotransported into cells. Its cytotoxicity might come from its DNA binding. However, resistance and toxicity soon became known.

Other Pt(II)-derived complexes were obtained by derivatization processes from cisplatin. And potential new agents with better anticancer and pharmacokinetic properties became known; a few examples are shown in Fig. 5.7 (Nadgi et al. 2017; Johnstone et al. 2015).

Carboplatin was also FDA approved and used in situations of ovarian cancers. Its toxicity is lower than the one given by cisplatin. It was used in combination with other chemotherapeutic agents like oxaliplatin against colon, pancreatic, and gastric cancers.

Picoplatin has demonstrated interesting properties in a resistant cisplatin cell line; it is still under clinical evaluations in phases I and II.

Aroplatin is another potential drug to be used in liposomal formulations. It demonstrates to have higher biocompatibility and drug loading with pharmacokinetic properties.

Nedaplatin is another anticancer Pt(II) derivative which was approved in Japan in 1995. It has revealed safer medicinal profiles than cisplatin against urological tumors.

Lobaplatin is another anticancer drug with action against several types of malignancies. Positive results were obtained under leukemia situations. It is still under clinical trials in other situations. But it is approved in China against leukemia, breast, and lung cancers.

Phenanthriplatin is a monofunctional complex in its DNA binding, which has revealed better cytotoxic effect than cisplatin.

All these Pt(II) derivatives were developed by taking into consideration the negative biological properties meanwhile demonstrated by cisplatin.

As already stated some of them have shown significant biological anticancer properties, other still are under clinical trials and other ones have been discontinued (e.g., aroplatin).

The anticancer research in the platinum field has been also extended to the Pt(IV) derivatives. Such compounds are six-coordinated derivatives with octahedral geometries. Such properties might bring a better stability for such complexes with improved cytotoxicity features.

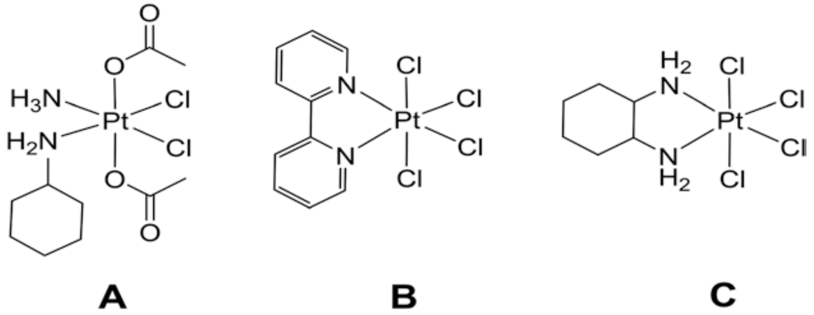


Fig. 5.8 Pt(IV) complexes under investigation

The first Pt(IV) complex with success is satraplatin (**A**, Fig. 5.8). Its activity is positive against several types of cancers, but it is under clinical trials against prostate cancer. It can be taken orally.

Two other Pt(IV) complexes (**B** and **C**, Fig. 5.8) are under investigation against colon cancers.

5.2.2 Ruthenium

Ruthenium (Ru) is a transition metal species of the iron chemical group, which has been considered in anticancer research procedures. It has two oxidation states (II and III) which make possible the synthesis and biological evaluation of several stable Ru complexes. However, it has been established that the Ru(III) derivatives are active upon their reduction to the Ru(II)-state. Ru(IV) derivatives are also potential possibilities, but they lack adequate stability. In such way, the development of synthetic strategies has been taking place for Ru(II) and Ru(III) compounds.

The following examples (Fig. 5.9) are Ru(III) complexes which were the first ones to be approved for clinical trials. The antitumor activity of KP418 became known in 1986 (Alessio and Messori 2019). Afterwards the Ru(III) imidazole derivatives known as NAMI-A and the indazole derivative KP1019 or its more soluble sodium salt KP1339 were then developed. Such derivatives are under clinical evaluation.

Obviously studies involving Ru(II) derivatives have also been carried out. Applications in several areas for Ru(II) derivatives became known, and so the Ru(II) chemistry has been the subject of many publications.

For the oncological area, several compounds were synthesized and their cellular uptake and cell death processes were clarified (Zeng et al. 2017). But further biological assessment is required to reach the drug target step.

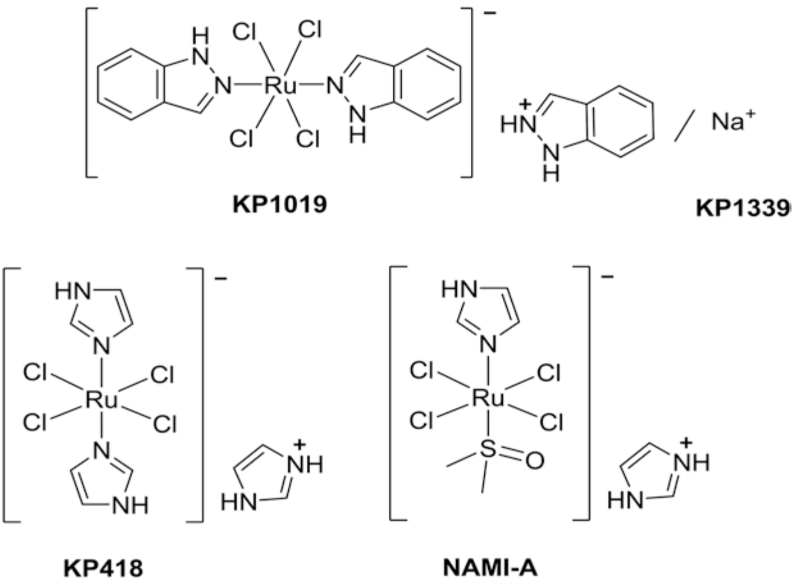


Fig. 5.9 Ru(III) coordination compounds as anticancer drug candidates

5.3 Final Remarks

As it is known, our life and health situation depend on the action of several metal species. Their association with other biological entities allows “the living organisms to live.” Certainly, biological events like respiration, photosynthesis, and drug detoxification are vital functions ruling life. Obviously without the adequate metal complexes, there would be no such functions and life whatever it could be would be totally different from the one taking place in our planet. But the desired improvement on life conditions will continue to depend on further research involving metal ions for the development of new anticancer drugs.

References

Alessio E, Messori L (2019) NAMI-A and KP1019/1339, two iconic ruthenium anticancer drug candidates face-to-face: a case story in medicinal inorganic chemistry. Molecules 24:1995–2014

Baile MB, Kolhe NS, Deotarse PP, Jain AS, Kulkarni AA (2015) Metal ion complex potential anticancer drug: a review. Int J Pharma Res Rev 4:59–66

Denisov IG, Sligar SG (2010) Cytochrome P450 enzymes. In: Kadish KM, Smith KM, Guilard R (eds) Handbook of porphyrin science. Word Scientific, Singapore, p 165

Fang H, Kang J, Zhang D (2017) Microbial production of vitamin B_{12}: a review and future perspectives microb. Cell Fact 16:15–28. https://doi.org/10.1186/s12934-017-0631-y

Johnstone TC, Suntharalingam K, Lippard SJ (2015) Third row transition metals for the treatment of cancer. Philos Trans A Math Phys Eng Sci 373: 2037 https://doi.org/10.1098/rsta.2014.0185. Philos Trans R Soc A 373: 20140185

Kendrew JC, Bodo G, Dintzis HM, Parrish RG, Wyckoff H (1958) A three-dimensional model of the myoglobin molecule obtained by x-ray analysis. Nature 181:662–666

Lieu PT, Heiskala M, Peterson PA, Yang Y (2001) The roles of iron in health and disease. Mol Asp Med 22:1–87

Lippard SJ, Berg JM (1994a) Principles of bioinorganic chemistry. University Science Books, p 288

Lippard SJ, Berg JM (1994b) Principles of bioinorganic chemistry. University Science Books, p 307

Milgrom LR (1997) The colours of life. Oxford University Press, Oxford, p 116

Nadgi U, Mhlongo N, Soliman ME (2017) Metal complexes in cancer therapy – an update from drug design perspective. Drug Des Dev Ther 11:599–616

Ordway GA, Garry DJ (2004) Myoglobin: an essential hemoprotein in striated muscle. J Exp Biol 207:3441–3446. https://doi.org/10.1242/jeb.01172

Rosenberg B, Van Camp L, Krigas T (1965) Inhibition of cell division in Escherichia coli by electrolysis products from a platinum electrode., Nature 205 (4972): 698–699. https://doi.org/10.1038/205698a0.. PMID14287410

Sheldon RA (1994) Metalloporphyrins in catalytic oxidations (Ed. RA Sheldon). Marcel Dekker, New York, p 11

Silva G, Pires SMG, Silva VLM, Simões MMQ, Neves MGPMS, Rebelo SLH, Silva MAS, Cavaleiro JAS (2014) A green and sustainable method for the oxidation of 1,3-dihydrobenzo[*c*]thiophenes to sulfones using metalloporphyrin complexes. Catal Commun 56:68–71

Simões MMQ, Neves CMB, Pires SMG, Neves MGPMS, Cavaleiro JAS (2013) Mimicking P_{450} processes and the use of metalloporphyrins. Pure Appl Chem 85:1671–1681. https://doi.org/10.1351/PAC-CON-12-11-15

Stryer L (1981) Biochemistry, 2nd edn. W.H. Freeman, San Francisco, p 49

Williams RJP, Fraústo da Silva JJR (1996) The natural selection of the chemical elements. Clarendon Press, Oxford, p 553

Zeng L, Gupta P, Chen Y, Wang E, Ji L, Chao H, Chen ZS (2017) The development of anticancer ruthenium(II) complexes: from single molecule compounds to nanomaterials. Chem Soc Rev 46:5771–5804. https://mineralseducationcoalition.org/elements/magnesium/

Chapter 6
General Data on Clay Science, Crystallochemistry and Systematics of Clay Minerals, Clay Typologies, and Clay Properties and Applications

Celso S. F. Gomes and Michel Rautureau

Abstract Clay and clay minerals are ubiquitous constituents of the Earth's crust, and they are being used by man for therapeutic, cosmetic and many other basic purposes, for instance, in pottery and construction, since prehistoric times. Clay and clay minerals are unique within all other minerals, and as, natural and fine-grained materials they are characterized by singular specific properties such as plasticity and absorption. Also, they are the main constituents of clayey soils and edible clays object of geophagy practices, and of healing mud and peloids used in mud therapy and pelotherapy. This chapter is initiated with relevant information, mainly on clay science, clay and clay minerals' definition, clay typologies, crystallochemical characteristics and properties of clay minerals' species as well as clay typology. Clay minerals' specific properties, such as electric charge (cationic and anionic clay minerals), active sites and functional groups in clay mineral surfaces, basic structural units, planar and non-planar structures and systematic of clay minerals are presented and discussed. The unique properties of certain clays and clay minerals justify their uses for both internal and external applications, in medicines, pharmaceuticals and cosmetics.

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

M. Rautureau
Docteur d'État ès Sciences Physiques, Retired of University of Orléans, Orléans, France
e-mail: mrautureau@wanadoo.fr

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_6

6.1 Introduction to Clay Science

According to Wagner et al. (1998), Carretero et al. (2002, 2006), Wilson (2003) and De Vos (2010), both animals and humans have used *clay*, *clay minerals* and other *minerals* for therapeutic purposes since prehistoric times. Also, cases of *healing clays* have been documented (Droy-Lefaix and Tateo 2006; Carretero et al. 2006; Rautureau et al. 2017). The authors referred to have reviewed the available studies of the beneficial effects of clay and clay minerals on gastrointestinal illnesses attributed to the adsorption of microbes, viruses or their toxins and modification of the mucus lining reinforcing natural defences of the gastric tissue. The beneficial effects could be also favoured by the supply of nutritional *mineral supplements* (e.g. Fe and Cu) that could be provided by certain clay minerals (Aufreiter et al. 1997; Kikouama et al. 2009, Kikouama and Baldé 2010).

Clay, as a natural material, is the main constituent of soils object of *geophagy* practices, also of "*edible clays*", and yet of *healing muds* and *peloids* used in *mud therapy* and *pelotherapy*. Clay is a unique mineral within all minerals. Thorez (2003) has called clays "the mutants of the mineral world" because they are able to change their chemical makeup via ion exchange and readjust to the environment due to their small particle size (<2 μm) and large reactive specific surface area (>100 m^2/g), reactivity due to the electric charge of clay minerals, the clay fundamental constituents.

Some relatively rare natural clays and clay minerals have been identified by their ability to kill a variety of pathogenic bacteria (Williams et al. 2004, Ma'or et al. 2006; Haydel et al. 2008). That is the case, for instance, of the so-called French green clays, mainly composed of *1Md illite* and *Fe-smectite* that successfully have been used to heal *Buruli ulcer*, a necrotizing or "flesh eating" mycobacterial infection (Brunet de Courssou 2002). However, the bactericidal character never happens in clay and clay minerals' dry state, always requiring hydration state. Some other natural clays and clay minerals require adequate manipulation to perform bactericidal properties.

In the literature, we can find interesting references to clay acting as health healing and protector material. Rautureau et al. (2017) report the interesting fact that French soldiers in the First World War who had received mustard (a condiment containing a small quantity of clay as a jellifying agent) in their food ration were less subject to the effects of dysentery and other prevalent diseases within the armies in the field.

Bentonite, *kaolin*, *fibrous clay* (*sepiolite* and *palygorskite*), *French green clay* and *nanoclay* are the most interesting clay types for medical, pharmaceutical and cosmetic applications. Regarding clay, a mineral substance widely used in geopharmacy and geotherapeutics, there is much more or less recent scientific information.

The benefits of clays to human health are well documented in several recently published articles: Robertson (1986, 1996), Novelli (1996, 1998, 2000), Reinbacher (1999, 2003), Viseras and Lopez-Galindo (1999), Veniale (1996, 1998, 1999), Carretero (2002), and Veniale et al. (2004). Also, books of a general scope document too such benefits, and the authors of some of them are herein mentioned: Selinus et al. (2005), Gomes and Silva (2007), Carretero and Pozo (2007), Rautureau et al. (2010, 2017).

All the articles and books referred to disclose important information about properties, applications and functions of clay, clay minerals and clay-based products in human health. Many other studies showing the healing properties of clays and clay minerals are well documented in further topics of this chapter.

The aforesaid justifies the need to provide relevant information, mainly on Clay science, clay and clay minerals' definition, clay typologies, crystallochemical features and systematics of clay minerals and properties of both clay minerals and clays.

Today, when nanotechnology is the hallmark of the scientific world, the so-called nanoclays are fundamental raw materials for several essential technological applications. As a matter of fact, clay of the nanoclay typology has important applications in technological fields, such as *catalysis* (Garrido-Ramirez et al. 2010; Nagendrappa 2011), *food packaging* (Azeredo 2009; Majeed et al. 2013), *textile industry* (Floody et al. 2009; Shahidi and Ghoranneviss 2014) and *high strength materials with thermal and gas barrier properties* (Liu et al. 2011; Wu et al. 2014; Gamelas and Ferraz 2015). Besides these applications, nanoclay has specific and other rather important applications in fields such as *medicine* (Ambre et al. 2010; Suresh et al. 2010), *cosmetics* (Patel et al. 2006; Carretero and Pozo 2009, 2010) and *pharmacy* (Carretero and Pozo 2009, 2010; Khurana et al. 2015). In the particular case of the pharmaceutical industry, clay minerals are widely used as lubricants, desiccants, disintegrants, diluents, thickeners, emulsifiers, binders, pigments, opacifiers, flavour correctors, carriers of active ingredients and anticaking agents.

Other unique clay mineral features are electric charge, specific surface area, dispersivity, hygroscopicity, unctuosity, thixotropy, plasticity, cation exchange capacity, sorption and desorption capacity and varied colour (Khurana et al. 2015). These same authors have synthesized in tables the pharmaceutical activity of certain clay minerals and of certain other minerals; they also propose the corresponding mechanisms of action as well as the applications of natural clay minerals in drug delivery.

Clay minerals need to undergo modification and functionalization of their particle surfaces before incorporation into polymer matrices to develop polymer-clay nanocomposites. As a consequence of clay minerals' electric charge, in general, they show hydrophilic character turning them incompatible with a wide range of polymer types. However, organophilic clay minerals can be produced by ion exchange with an organic cation. For instance, in *Na^+-montmorillonite*, sodium ions can be exchanged for an amino acid such as 12-aminododecanoic acid (ADA) to turn the clay mineral hydrophobic and therefore more compatible with polymers.

Nanoclay high specific surface area is an important factor, since higher surface areas facilitate the interaction clay-polymer. Refining, i.e. going from micro- to nanoscale, and delamination or exfoliation of the platy particles of clay minerals, such as *kaolinite* and *montmorillonite*, could much increase their specific surface areas and consequently the exposure to the polymer matrix. In all applications, nanoclay improves the product quality, costs economy and environment safety.

Khurana et al. (2015) made a special report on clay minerals providing a bird's-eye view of the chemical composition and structure of these minerals and their influence on the release properties of active medicinal agents or drugs. Nanoparticles of other materials are currently available, such as aluminium oxide, copper oxide, iron oxide, titanium dioxide, zinc oxide and calcium carbonate.

According to Rautureau et al. (2017), any science, scientific field or scientific domain requires a well-established and defined object of study, as well as appropriate methodologies to develop the knowledge about that object. However, along the time the definition or concept of the object of study can undergo modifications and adaptations due to science advances, both in theoretical and experimental terms.

Bergaya et al. (2006) consider clay science, i.e. the study of clay, a relatively young discipline initiated about 100 years ago, and the authors enlighten the most remarkable stages of its historical development, and remarkable are too the many references the authors disclose concerned with the subject.

Clay science is multidisciplinary having as objects of study both clay and clay minerals, their properties and applications. It receives important contributions from other sciences or disciplines, such as mineralogy, crystallography, chemistry, geochemistry, sedimentology, geology, paedology, agronomy, soil mechanics, colloid chemistry, materials science, biology and biotechnology, medicine and public health, pharmacy, geoengineering and environmental engineering. As in other sciences, the object or objects of study referred to require a definition that would deserve the general acceptance by all those interested on it, both theoretically and practically, despite the reckoned historical evolution of the concepts.

Differently of what happens in other sciences, the enormous clay diversity in geological, compositional (physical, chemical and physicochemical) and technological terms, as well as the enormous diversity of clay fields of interest and applications, might justify the lack of consensus on clay and clay mineral definitions that will be shown along this chapter.

Clay science is less than 100 years old, and along its evolution, the definition of clay and clay mineral, the objects of study of this science, has shown significant changes that have been proposed, developed and adopted by several authors and clay groups or clay societies. Such changes were based not only on basic but selective criteria very much dependent upon the particular academic education and professional experience of the authors, for instance, soil scientists, mineralogists, geologists or materials scientists.

Clay Minerals Society (CMS) with headquarters in Chantilly, Virginia, USA, founded in 1962, has as primary purpose to stimulate research and education and to disseminate information relating to all aspects of clay science and technology. CMS uses to organize annual meetings (AM), which are international multidisciplinary conferences about clay minerals research, applications and technology developments in different disciplines. CMS members include mineralogists, crystallographers, physicists, chemists, geochemists, soil scientists, agronomists, ceramic scientists, civil engineers, petroleum geologists and engineers and industrial scientists. In 2014, the society had about 700 members, one-half of whom are from countries outside the USA. All CMS members belong to the AIPEA (Association

Internationale Pour L'Étude des Argiles) created in 1966, an entity that gathers the individual members of the existing 23 national clay groups from all over the world.

Through the conferences and publications, the journal *Clays and Clay Minerals* and Workshop Lectures Series, CMS provides numerous opportunities for the information exchange and interdisciplinary research collaboration. The last two annual meetings were held, the 55th at the University of Illinois at Urbana-Champaign, and the 56th at the University of Pierre and Marie Curie, in Paris. These conferences, as a rule, are dedicated to particular themes, e.g. "New Visions of Clay Science" in the case of the 55th AM, and 19 thematic sessions covering a broad range of clay sciences: clay mineralogy, crystallography, petrology, materials science, nanosciences, bio-nanoclays in medicine, environmental engineering, soil science, biogeochemistry, industrial technology, isotope geochemistry, cosmogeochemistry, advanced spectroscopies and education, having attracted 240 abstracts. The first proceedings of the AM conferences was issued in 1952. These conferences, as a rule, are attended by hundreds of worldwide clay scientists.

As regards the Workshop Lectures Series, 22 volumes have been already published, the first volume dated of 1989 and entitled "Quantitative Mineral Analysis of Clays", Pevear JR and Mumpton being the editors, and the last volume entitled "Introduction to Oil Sand Clays", Omotoso O and Hockley D being the editors.

In Europe, the Mineralogical Society of Great Britain & Ireland edits the journal *Clay Minerals* in conjunction with the European Clay Groups Association (ECGA). Clay Minerals have continued the *Clay Minerals Bulletin* (1947–1964), and presently the journal produces four issues/year. The Mineralogical Society of Great Britain & Ireland produces monographs too.

Also, in Europe, the national clay groups organize regular scientific meetings, scientific publications being the normal outcome of them. In Europe, the European Clay Groups Association (ECGA) created in 1987 uses to organize quadrennial conferences; the last one, the Euroclay 2019, being organized by the Groupe Francais des Argiles (GFA), was held at the University of Pierre and Marie Curie, in Paris, under the auspices of ECGA and AIPEA (Association Internationale Pour L'Étude des Argiles).

The 56th Annual Meeting of ACS and the 6th Mediterranean Clay Meeting (MCM) were associated to the Euroclay 2019 Conference. The 57th CMS Annual Meeting will be held in Istanbul, Turkey, jointly organized with Turkish Clay Group. The 58th CMS Annual Meeting will take place in Richland, Washington, USA.

The progressive advances on clay science are general or specialized targets and subjects of several publications, books and journals. Within the books, the nine issues or volumes of a series entitled *Developments in Clay Science* are examples of publications that deserve particular appreciation by the clay scientists. A recent article by Zhou et al. (2016) makes clear the highly significant current developments on clay science in China.

Clay occurs where we less expect, not only in rocks of any type (sedimentary, igneous and metamorphic), but also dispersed in atmospheric aerosols, and suspended in the water of oceans, seas, lakes, lagoons and rivers. Naturally and industrially produced dusts that could have deleterious effects on human health can contain clay minerals too.

The basic subject of clay minerals genesis is excellently dealt with in Gálan (2006). Clay minerals are spatially distributed from deep within the Earth's crust to the Earth's surface and to Martian landscapes (Johnston 2010; Milliken and Bish 2011). As a matter of fact, clay minerals are not unique to Earth. The Mars Exploration Rovers, the Mars Phoenix Scout and the Mars Science Laboratory (MSL) have identified hydrous phyllosilicates (clay minerals), sulphates, carbonates, Fe-oxyhydroxides and other minerals at several landing sites. A group of 19 researchers have determined and shown the first X-ray diffraction analyses of clay minerals on Mars; illite and smectite have been identified (Vaniman et al. 2014).

The Mars Science Laboratory rover, named *Curiosity*, carried CheMin, the first X-ray diffraction (XRD) instrument used on a planet other than Earth. With CheMin, the first direct sampling and characterization of clay minerals on Mars could be obtained. Also, in terrestrial laboratories, clay minerals could be identified too in samples of Martian carbonaceous chondrite meteorites.

Clay science, as any science has a past, has a history, and its memory is the required foundation for present and future developments. Within the distinguished and brilliant clay scientists pioneers of clay science. In the 1960s, when one of the authors (CSFG) of this book was just initiating his learning and research in clay science, he had the honour to personally meet, listen and talk with them, particularly during scientific meetings; some of them deceased, are herein remembered: Ralph Grim (1902–1989) from the University of Illinois, Urbana, USA; George Brindley (1905–1983) from the Pennsylvania State University, USA; Jackson ML (1914–2002) from the University of Wisconsin, Madison, USA; Sturges William Bailey (1919–1994) from the University of Wisconsin, USA; William D Keller (1900–2001) from the University of Missouri, USA; Haydn Herbert Murray (1924–2014) from the Indiana University; Robert Mackenzie (1920–2000), Victor Colin Farmer (1920–2006) and Jef Wilson from the Macaulay Institute for Soil Research, in Aberdeen, Scotland; George Brown (1926–1996) from the Soils and Plant Nutrition Department, Rothamsted Experimental Station, Harpenden, England; Simone Caillère (1905–1999) from the Laboratoire de Minéralogie, Muséum National d'Histoire Naturelle, Paris, France; Robert Robertson (1911–1999) from the Cambridge University, England; Georges Millot (1917–1991) from the Université de Strasbourg, France; Carl Wilhelm Correns (1893–1980) from the Kaiser Wilhelm Institute of Physical Chemistry, Berlin, Germany; Karl Jasmund (1913–2003) from the University of Rostock, Germany; Armin Weiss (1927–2010) from the University of Munich, Germany; Toshio Sudo (1911–2000) from the Tokyo University of Education, Japan; Boris Zvyagin (1921–2002) from the Institute of Ore Mineralogy of the Russian Academy of Sciences, Moscow, Russia; Jiri Konta (1922–2017) from the Charles University, Czech Republic; José Serratosa Márquez (1924–2012) from the Instituto de Edafologia del CSIC, Madrid, Spain; Emilio Galán Huertos (1932–2018) from the University of Seville, Spain; Fernando Veniale (1929–2019) from the University of Pavia, Italy; Lisa Heller-Kalai from the Hebrew University, Jerusalem, Israel; Pérsio de Souza Santos from the University of São Paulo, Brazil; Gerhard Lagaly from the University of Kiel, Germany; Maria Franca Brigatti from the University of Modena, Italy; Faïza Bergaya from the University of Orléans, France; Benny Theng from Landcare Research, New Zealand; Peter Komadel from the Institute of Inorganic Chemistry, Slovakia; Jose Luis Pérez Rodriguez from the University of Seville, Spain; Maria Isabel Carretero from the University of Seville, Spain; Alberto Lopes Galindo from the University of Granada, Spain; Fabio Tateo from the Instituto di Ricerca sulle Argille, Italy; Eduardo Ruiz-Hitzky from the Instituto de Ciencia de Materiales de Madrid, Spain; and some others.

When the optical microscope was the only instrumental tool to analyse geological materials, that is, during the last decades of the nineteenth century and the first decades of the twentieth century, clay was defined as an association of fine-grained minerals with particle diameters of less than 2 μm, i.e. beyond the resolution of the optical microscope. Earlier chemical analysis became a fundamental tool to determine the chemical composition of both clays and clay minerals, allowing the establishment of their typology.

Soil science, colloidal chemistry and the development of analytical techniques, such as differential and gravimetric thermal analysis and transmission and scanning electron microscopy, have contributed very much for the identification, quantification and explanation of clay and clay minerals' basic properties.

Starting with the third decade of the twentieth century, X-ray diffraction (XRD) became a powerful tool for investigating the structure of fine-grained materials, clay minerals included, allowing the differentiation of clay mineral structures' achievement fundamental to explain their distinctive properties. As a matter of fact, clay minerals that have been considered essentially amorphous materials, step by step, were found to be structurally ordered and diversified too in physical and chemical properties.

The 60s decade, in particular, really was a golden epoch of clay research due to the dissemination in the USA, Europe and Japan of appropriate analytical systems, in particular based on X-ray diffraction and electron diffraction.

Several other analytical systems soon became available, such as transmission electron microscopy (TEM) with the mode high-resolution imaging (HRTEM), scanning electron microscopy (SEM) associated to X-ray energy-dispersive spectrometry (EDS) to determine the composition of inorganic species, electron energy-loss spectrometry (EELS) to measure the concentration of heavier elements than Li, their oxidation states and chemical speciation; selected area electron diffraction (SAED), electron tomography (ET) to determine 3D particle shapes, and synchrotron X-ray diffraction (SR-XRD).

Modern instrumentation and analysis of clay minerals will play essential roles in modern clay research that is essential to a full understanding of the genesis, role and potential new uses for clays and clay minerals, focused on processing and modifying of clay minerals in order to participate in new adsorbents, catalysts and biomaterials. Indeed, advanced clay-based nanomaterials create great expectations for the use of clay minerals in new approaches to sustainable energy, green environment and human health.

These new facilities and the increasing number of clay researchers with education on both fundamental and applied fields of mineralogy, crystallography, physics, chemistry, geochemistry, soil science, agronomy, ceramics, civil engineering, industrial minerals, mineral oil and gas geology and engineering, materials science, nanomaterials, environmental science and health science have contributed for the progressive increase of the number of annual publications.

The identification and characterization of clay minerals based on X-ray analysis (both structural and chemical), thermal analysis (both gravimetric and differential) and infrared spectra analysis have beneficiated of the excellent and indispensable contributions, under the form of textbooks or chapters of books by Grim (1953, 1962, 1968), Kübler (1964, 1968), Jackson (1956), Worrall (1975, 1982), Thorez (1975, 1976), Caroll (1979), Bailey (1980a, b), Caillère et al. (1982, 1989), Brindley and Brown (1980), Chamley (1989, Wilson (1987, 2003, 2013), Velde (1992), Meunier (2005), Brigatti et al. (2006), Murray (2006).

In the fields of clay mineralogy, geology, geochemistry, genesis, properties, as well as in the fields of industrial, environmental and medicinal applications, some relevant textbooks and book chapters are herein mentioned: Kubler (1964), Millot (1970), Worrall (1975, 1982), Grim and Guven (1978), Wilson (1987), Chamley (1989), Veniale (1996), Murray (2006), Christidis (2011).

Wang and Wang (2019), editors of the book *Nanomaterials from Clay Minerals: A New Approach to Green Functional Materials* published by Elsevier, in the book preface after consulting the database of the Web of Science, mention that in 2018 the number of publications involving research on clays and clay minerals was estimated in 8167.

Notwithstanding the Clay science being a recent scientific field, effectively created in the initial years of the twentieth century, counting 15 publications in 1915 and 600 in 1990, it had particularly flourished after 1990. Dozens of periodicals publish the results of the research being produced, the scientific journals *Clays and Clay Minerals*, *Clay Minerals*, and *Applied Clay Science* being the most notorious.

A particular reference deserves the series of handbooks on *Developments in Clay Science* produced by Elsevier Ltd, dealing with various scientific areas and topics of clay science, the first book of a total of nine was issued in 2006, and the last one in 2018.

6.2 Concepts of Clay and Clay Mineral

Both AIPEA and CMS Nomenclature Committees have been involved along the years in the definition, classification and terminology of clays, clay minerals, related materials and specific properties. For instance, the AIPEA Nomenclature Committee has proposed over the years several reports with recommendations: Brindley and Pedro (1970, 1976), Bailey et al. (1986), Bailey (1989), Guggenheim et al. (1997), Guggenheim et al. (2002), and Guggenheim et al. (2006).

Recommendations have been proposed too in joint reports of AIPEA and CMS Nomenclature Committees (Guggenheim and Martin 1995, 1997) and by the CMS Nomenclature Committee (Bailey et al. 1971a, b; Bailey et al. 1979; Martin et al. 1991).

Despite the continued efforts of the Nomenclature Committees referred to, the definitions of *clay* and *clay minerals* still are not unanimous. Such could be understood because, for instance, clay being most probably the mineral resource exhibiting the highest variability in geological, textural and mineralogical terms and the most diverse applications, either the professionals, or the disciplines interested on clay try to enhance in its definition the property or properties of clay which are relevant for a particular application, situations well expressed in Gomes (1988, 2002) and in Rautureau et al. (2017):

1. *Geologists* consider *clay* as a geological product of generalized occurrence and of fine granularity that occurs at the surface or near the surface of the Earth and that is formed at the interfaces between the Earth's crust and the atmosphere, hydrosphere and biosphere as the result of the mechanical and/or chemical alteration of rocks; also, *geologists* classify clays on the basis of their origin and occurrence: residual or primary and sedimentary or secondary (marine, alluvial, glacial, and eolian).
2. *Mineralogists* consider *clay* as an aggregate or mixture of minerals of fine granularity, consisting principally of clay minerals, which are hydrous phyllosilicates based on Si, O, OH and H_2O, and elements such as Al, Mg, Fe, K, Ca and Mg can participate on their composition.
3. *Petrologists* consider *clay* as a rock, as a rule weakly consolidated, formed by very fine mineral particles non-identifiable at naked eye or using a magnifying glass.
4. *Sedimentologists* consider *clay* as a granulometric term that identifies the sediment fraction composed of particles with ESD (equivalent spherical diameter) less than 2 μm.
5. *Civil and geotechnical engineers* consider *clay* as the less than 4 μm fraction of the soil and classify clays or clayey soils as swelling or non-swelling, soft or hard, that is selecting the most relevant properties that should be taken into account when the foundation of housing and public construction works is based on them.
6. *Ceramists* consider *clay* as a natural geological material that whenever mixed with water in adequate quantity becomes plastic allowing its workability and shaping and that hardens and maintains the acquired shape after drying or firing; ceramists classify clays on the basis of their plasticity, firing properties and uses: low plasticity, medium plasticity, high plasticity; white burning, red burning, high or low refractory; common clay (brick and roof tile clay and pottery clay); special clay (china clay, fire clay, flint clay, ball clay, bauxitic clay, fibrous clay).
7. *Paedologists* consider *clay* as the active fraction of the soil that comprises particles of colloidal size (<0.1 μm) that results from the action of paedological pro-

cesses upon rocks, and which are responsible for the reversible fixation of cations and anions, such as NH_4^+, K^+, PO_4^{3-} and NO_3^-), etc.

8. *Agronomists* consider *clay* as the colloidal fraction of the soil, important in terms of structure, texture and composition for vegetal fixation and growth.
9. Even the *non-educated people* consider *clay* as a type of earth that gets slippery when wet and that could be moulded or shaped.

From the aforesaid clay concepts, it is clear that concepts in science can be expressed differently by people from different educational backgrounds and experiences. Concepts can also evolve over time.

Gomes (2002) has distinguished three basic concepts in the field of clay science: *clay*, *clay mineral* and *clayey material* or *clay-bearing material*.

Clay is "a natural material, mostly composed by fine-grained minerals, mainly hydrated phyllosilicates the so-called clay minerals; clay, in general, exhibits plastic behaviour and hardens after drying or firing; associated to clay minerals other minerals and non-minerals (inorganic and organic cryptocrystalline or amorphous compounds) can occur in clay".

Clay minerals are "phyllosilicates, essentially hydrous aluminosilicates, fundamental constituents of clay and accessory constituents of clayey rocks and clayey soils, responsible for clay plasticity and hardening after drying and firing".

Clayey materials or clay-bearing materials are "those geological materials, such as shale, slate, phyllite, marl, marly limestone, lapilli tuff, hyaloclastite tuff, and soils that could bear clay minerals in significant quantity; despite of some of these materials do not exhibit plasticity in the natural state they could be used, for instance, as ceramic raw materials after being finely ground or blended with other adequate minerals".

Distinctive parameters for clay and clay mineral should be taken into account in their concepts, well summarized by Bergaya and Lagaly (*in Handbook of Clay Science*, Elsevier, 2006):

> For clay: "Natural; fine-grained (<2 μm or <4 μm); phyllosilicates as main constituents; plastic; hardens on drying or firing".
>
> For clay mineral: "Natural and synthetic; any size; may include non-phyllosilicates; plastic; hardens on drying or firing".

Very recently, Moreno-Maroto and Alonso-Azcárate (2018), soil specialists, state that particle size criterion is not proper to differentiate clays, clayey materials and non-clayey soils while plasticity is. Plasticity is defined as "the ability of a material to be molded to any shape". Plasticity is a fundamental property in the processing of clay- based materials since it defines the technical parameters to convert a ceramic mass into a given shape by application of pressure (Moore 1965). Plasticity in clay-water systems is defined as the "property of a material which allows it to be repeatedly deformed without rupture when acted upon by a force sufficient to cause deformation and which allows it to retain its acquired shape of the removal of the applied force (Perkins 1995). Several measuring techniques and devices can be used to determine the plasticity of clay-water systems, such as: Atterberg method, Pfefferkorn method, penetration methods, Capillary rheometer method, Torque rheometer method (Andrade et al. 2011). Mineralogical composition, particle size distribution, water nature and content, and organic substances nature and content are the major conditioning factors of clay-water plasticity.

Guggenheim and Martin (1995) state that in the case of clays, the plasticity is provided by clay minerals. It is well known that different species of clay minerals provide different plasticities, and such determines the minimum clay minerals' total content (as a rule >10%) that allows the classification of a geological material as a clay.

Moreno-Maroto and Alonso-Azcárate (2018) have put forward a new definition of *clay* based on plasticity, the ratio plasticity index/liquid limit (PI/LL) being a great indicator that soil and clay scientists could use to classify soil textures based on PI/LL ratio and sand percentage. A fine-grained material can be defined as a *clay* when $PI \geq LL/2$ and a moderately or slightly clayey material if $LL/3 < PI < LL/2$ (LL being the Atterberg liquid limit). The authors propose the following definition for clay:

"A naturally occurring material composed primarily of fine-grained minerals whose PI is equal to or higher than LL/2, so that a clay is plastic or highly plastic at those water contents located between the LL and PL. A moderately or slightly clayey material is a naturally occurring material composed primarily or partially of fine-grained minerals, whose PI value is between LL/3 and LL/2, so that a clayey material is slightly or moderately plastic at those water contents located between the LL and PL. Both clayey materials will harden when dried or fired, being this effect more pronounced as the value PI/LL increases".

"Flint clay", also called "hard clay", is a type of *clay* that can contain around 95% of clay minerals, and even so does not exhibit natural plasticity, unless after being very finely ground and mixed with an adequate content of water. Hence, the sole existence of clay minerals is an essential factor, but it is not a determining factor for a geological material to be classified as clay. Besides mineralogy, the geological history and diagenesis is also a conditioning factor.

The only factor able to definitively distinguish clay from non-clay geological materials is the existence of clay minerals in clay. But an important and decisive question remains concerning the clay concept. What is the less clay minerals' content able to allow the classification of a geological material as *clay*? Mineralogical composition, grain size and plasticity are complementary factors that could help to solve the question. With regard to clay minerals' definition, classification and nomenclature, over the times there has been some controversy too.

Clay minerals occur in rocks of all lithologies and ages. Also, clay minerals are common and important constituents of the fine fraction of *clay* as well as of the fine fraction of soils which are fundamental for life in general and for the human life in particular. Clay minerals are defined as "fine-grained hydrous phyllosilicates, minerals of planar or non-planar structures which could impart plasticity (if the right amount of water is added) and hardening (if dried or fired) to the clay in which they occur".

Clay may contain other materials that impart plasticity and harden when dried or fired. Clay minerals are not defined *a priori* as fine-grained minerals because clays are fine-grained materials, but rather they may be of any crystallite size so that the term clay mineral is consistent with the definition of mineral, which is unrelated to crystallite size. The particle size issue has been separated from the clay mineral definition.

What really characterizes and distinguishes mineral species, clay mineral species included, is their specificity in terms of chemical composition and structure (the way the constituent chemical elements like building blocks are spatially organized). However, the same chemical elements can be organized in different structures, the so-called polymorphs, as happens with the clay minerals *dickite* and *nacrite*, both polymorphs of *kaolinite*. As a rule, individual crystals of clay minerals exhibit micrometric sizes; in spite of some clay minerals, such as true micas, vermiculites and chlorites, they could exhibit millimetric and centimetric sizes.

Any clay has its own *clay fraction* in which the clay particles and clay minerals – the essential constituents of clay – are more concentrated. Conventionally, some disciplines set a maximum size for clay particles: paedology <2 µm; geology, sedimentology and geoengineering <4 µm; colloid science <1 µm. However, the upper limiting size of an individual particle or crystal for *clay minerals* has not been established.

Clay by definition is a geomaterial of natural occurrence mainly composed of fine-grained minerals, and within these minerals, the so-called clay minerals are essential or fundamental constituents. *Clay minerals* by definition are hydrous phyllosilicates that as a rule are characterized by plasticity exhibition, property observable as far as water is added to them in sufficient quantity, and by the property of getting hard after drying and firing.

Besides clay minerals, clay could contain silicates such as *quartz*, *feldspar* and *mica*; carbonates such as *calcite* and *dolomite*; iron and aluminium oxides and hydroxides such as *hematite*, *goethite* and *gibbsite*; X-ray amorphous organic materials such as organic matter constituted of several organic compounds; quasi-amorphous inorganic X-ray materials such as *opal A* and *ferrihydrite*; and amorphous iron hydroxides.

Man has used clay since the Neolithic initiated, approximately, at 10,000 years ago, period represented by polished stone and pottery. Ceramics is indeed the traditional field of clay application. The "Venus of Vestonice" found in 1920 in Dolní Vestonice, Moravia, Czech Republic, is the oldest known piece of baked clay, around 10 cm tall, and dated 23,000 years old. Within clay-based fragments of statuettes portraying wolves, horses, foxes, birds and women, the "Venus of Vestonice" is one of these prehistoric female figures that have remained almost undamaged. Another piece made of baked clay is the most recent archaeological find, the well-preserved bison found in the caves of Tuc d´Audoubert, in France, dated 12,000 years old.

Ceramics defined as man-made "nonmetallic inorganic solids" (Kingery et al. 1976) is classified into two classes: *traditional ceramics* and *advanced ceramics*, the first one based on baked or fired clay or pottery ware, the second one considered to be generally developed within the last 100 years.

Pottery ware is divided into two types: vitrified ware and nonvitrified ware, and within these divisions, we have distinct types: red paste pottery, and white paste pottery (earthenware, stoneware, porcelain of soft-paste and hard-paste, and bone china).

Advanced ceramics, also referred to as “special”, “technical” or “engineering” ceramics, exhibit superior mechanical properties, corrosion/oxidation resistance or electrical, optical and/or magnetic properties.

6.3 General Notes on Crystallochemistry and Systematics of Clay Minerals

By definition, as aforesaid, clay minerals are hydrous phyllosilicates of fine granularity and planar or non-planar structure that can provide plasticity to the clay in which they participate, if the right amount of water is added and afterwards dried and fired.

As phyllosilicates, clay minerals respective chemical formulas are based on the radical or anion $(Si_4O_{10})^{4-}$ or more simply $(Si_2O_5)^{2-}$, to which may be associated cations with Al^{3+}, Fe^{3+}, Fe^{2+}, Ca^{2+}, Na^+, K^+ and Li^+. As hydrated phyllosilicates, in the respective chemical formulas, water participates in the form of HO^- groups and/or H_2O water molecules.

In the ionic state, the chemical elements referred to above resemble small spheres that can be arranged or organized into seven distinct three-dimensional structural models characterized by a markedly two-dimensional development of the phyllosilicates. The ionic radii of the main anions and cations forming the clay minerals are generally expressed in picometres (1 pm ± 10^{-12}m), with the values of the ionic radii being the conditioning factors of the isomorphous substitution both between cations and between anions in the structures of the clay minerals.

At least some basic crystallochemical information is fundamental for an adequate understanding of the specific properties of clays and clay minerals, starting with the radii sizes of the principal chemical elements, anions and cations, which participate in their crystallochemical structures:

Anions:

O^{2-}, 140 pm; OH^-, 141 pm; F^-, 136 pm

Cations in the structural tetrahedral sheets:

Si^{4+}, 40 pm; Ti^{+4}, 68 pm; Al^{3+}, 51 pm; Fe^{3+}, 64 pm; Cr^{3+}, 69 pm

Cations in the structural octahedral sheets:

Mg^{2+}, 66 pm; Ca^{2+}, 99 pm; Fe^{2+}, 74 pm; Mn^{2+}, 80 pm; Zn^{2+}, 74 pm; Cu^{2+}, 72 pm

Interlayer cations:

Na^+, 97 pm; K^+, 142 pm; Li^+, 68 pm (interlayer spaces can be occupied too by cations that usually occupy *octahedral sites*)

6.3.1 Electric Charge of Clay Minerals

In clay minerals, as in other minerals, however to a greater degree and extent, justified by the conditions of their formation in terrestrial/hydrosphere/atmosphere/biosphere, interface environments characterized by large metastability, an electric charge is developed in their particles. Two types of electric charge exist in minerals: (1) a permanent charge resulting from higher valence cations replaced by lower valence cations or from atomic omissions in crystals structure; (2) a variable charge resulting from dissociation and/or association of protons by surface hydroxyl groups (Van Olphen 1963).

The so-called isomorphous atomic substitution in particular produces the appearance of an overall negative *electric charge* on the basal surfaces of clay particles whose value per unit cell varies according to the structure of the clay mineral species. For example, the clay mineral called *kaolinite*, $Al_2Si_2O_5(OH)_4$, shows the lowest value of *electric charge*, a little higher than zero, because the isomorphous atomic substitution is almost absent in this clay mineral of very simple chemical composition; the clay mineral *montmorillonite*, $(Na,Ca)_{0.33}(Al,Mg)_2(Si_4O_{10})(OH)_2nH_2O$, relative to kaolinite has a more complex chemical composition, and the electric charge shows values between 0.45 and 0.6; and the clay mineral called *illite* shows the highest value of electric charge, about 1.

Figure 6.1 shows a schematic representation of the electric charge distribution on clay mineral surfaces.

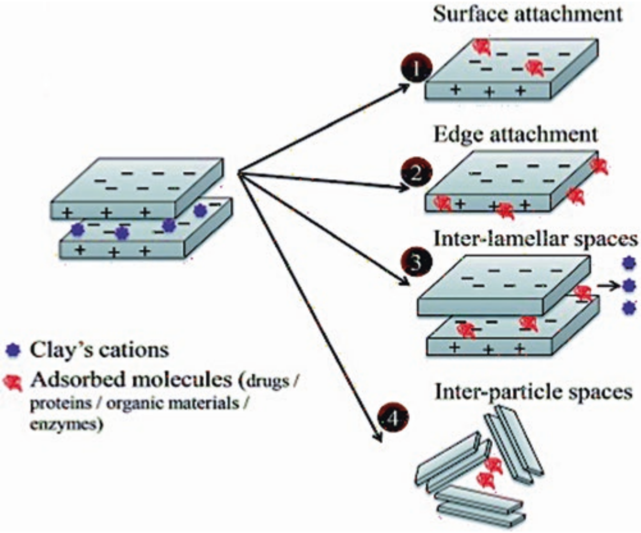


Fig. 6.1 Schematic representation of electric charge distribution in clay mineral surfaces (*In*: Ghadiri et al. 2015)

When dispersed in water, the electric charge distribution on clay mineral surfaces is very much influenced by the pH of the dispersion medium. Low pH turns particle edges positively charged and particle basal faces negatively charged conditions favourable to interparticle attraction. High pH turns particle edges negatively charged and particle basal faces negatively charged too, conditions favourable to interparticle repulsion. Neutral pH creates negative and positive charges on particle edges and negative charges on particle basal faces, conditions favourable to interparticle attraction and repulsion. The three situations referred to naturally control the stability or instability of clay/water dispersions.

Electric charge, particle size and particle shape are the fundamental properties of clay minerals, the other properties being dependent on them.

Paquet and Clauer (1997) established a simple systematic of clay minerals, based on the *electric charge* z of the structural unit, which comprises two main groups:

1. The group of low activity clay minerals, type 1:1 or T:O (one tetrahedral sheet linked to one octahedral sheet, in each structural layer), named *kaolinite group*, with electric charge $z \approx 0$ (as a rule, particularly in kaolinite, the electric charge value is little above zero due to very limited isomorphous substitution of Al for Fe or Mg, and Si for Al)
2. The group of high activity clay minerals, type 2:1 or T:O:T, named *illite/vermiculite/smectite group*, the electric charge z, as a rule, being less than 1

In group 1 the distribution of the basic chemical elements and the electric charge in the structural unit layer of kaolinite is shown in Table 6.1a.

In turn, group 2 comprises three categories:

(a) Category with high electric charge ($z = 0.8$–0.9) represented by *illite*
(b) Category with intermediate electric charge ($z = 0.45$–0.8) represented by *vermiculite*
(c) Category with low electric charge ($z < 0.45$) represented by *smectite*

In group 2, the distribution of the basic chemical elements and the electric charge in the case of *montmorillonite* structural unit layer is shown in Table 6.1b.

In real kaolinite and in the smectite group of clay minerals that includes *montmorillonite*, as well as in other clay minerals, the electric charge always exists due to

Table 6.1a Electric charge distribution in the structural unit layer of *kaolinite*

Electric charge distribution in the structural unit layer of *kaolinite*		
Ion	Number of ions	Total charge
O^{2-}	6	−12
Si^{4+}	4	+16
$O^{2-} + (OH)^-$	$4\ O^{2-} + 2(OH)^-$	−10
Al^{3+}	4	+12
$(OH)^-$	6	−6

Note: The plane of ions $O^{2-} + (OH)^-$ is shared by both tetrahedral and octahedral structural sheets

Table 6.1b Electric charge distribution in the structural unit layer of *montmorillonite*

Electric charge distribution in the structural unit layer of *montmorillonite*		
Ion	Number of ions	Total charge
O^{2-}	6	−12
Si^{4+}	4	+16
$O^{2-} + (OH)^-$	$4\ O^{2-} + 2(OH)^-$	−10
Al^{3+}	4	+12
$O^{2-} + (OH)^-$	$4\ O^{2-} + 2(OH)^-$	−10
Si^{4+}	4	+16
O^{2-}	6	−12

Note: The two planes of ions $4O^{2-} + 2(OH)^-$ are shared by the octahedral structural sheet and the two structural sheets

various types of crystal defects, those due to isomorphous substitution being the determinant ones.

Konta (1998) also on the basis of *electric charge*, but not only, considers five groups of clay minerals:

1. Low-medium electric charge clay minerals with structures of type 2:1 or T:O:T – the minerals of this group including *smectites* (low filler) and *vermiculites* (medium filler) incorporate solvated intercalated cations and have high absorbent capacity.
2. High electric charge clay minerals, in the case of *dioctahedral* and *trioctahedral micas*, which include unsolvated intercalated cations and having selective absorbing properties.
3. Uncharged or almost uncharged clay minerals: 1:1 or T:O; 2:1 or T:O:T; and 2:1:1 or T:O:T:O types of ores, such as *talc*, *pyrophyllite*, *kaolinite*, *serpentine* and *chlorite*, characterized by moderate absorbent and catalytic capacities.
4. Clay minerals with no electric charge with pseudocode structures, *palygorskite* and *sepiolite*, which have four different types of water, large microchannels and high absorbent capacity.
5. Amorphous or almost amorphous clay minerals, such as *allophane* and *imogolite*, which have high chemical reactivity and anionic adsorption.

The *electric charge* is usually determined in the clay minerals with expansive structure (*smectites* and *vermiculites*) by two methods:

1. One based on the exchange capacity of the alkylammonium cation.
2. Other based on the structural formula calculation.

Based on their *electric charge*, clay minerals can be divided into two groups:

1. *Cationic clay minerals* (cationic CM) which possess a general negative electric charge and are widespread in nature (e.g. *kaolinite* and *montmorillonite*).
2. *Anionic clay minerals* or layered double hydroxides (LDH) which possess a positive electric charge and are rarely found in nature, but rather simple and economical to synthesize.

From the applied point of view, the cationic clay minerals are much more interesting than the anionic clay minerals. In this regard, cationic clay minerals, both unmodified (natural and synthetic) and modified (clay-drug hybrid, organoclay, clay-polymer hybrid), have diverse applications in the fields of biological or biomedical systems, for example, in pharmaceuticals (as active ingredient, for instance, as drug carrier or as excipient), in cosmetics (for sunscreens and topical personal care), in biomaterials, in biosensors and in medical devices (Ghadiri et al. 2015).

6.3.2 Active Sites and Functional Groups in Clay Mineral Surfaces

The electric charge of clay minerals of type 2:1, besides being a very important criterion used in the systematic of this type of clay minerals, is also a property responsible for the chemical reactivity of its surfaces with certain organic and inorganic compounds and by the high water retention capacity for many clays and also indicative of the ability to set cations and adsorb water and several polar organic molecules. The said interactivity is concentrated on the surfaces of the crystals in the so-called active sites or functional groups which, for example, are decisive for the bactericidal character attributed to certain clay minerals and certain clays (Chap. 7, item 7.5 of this book).

Johnston (1996) considers six types of active sites or functional groups in clay minerals:

1. "Siloxane"-type surfaces in neutral hydrated phyllosilicates because they have an electric charge equal to zero or close to zero, being 2:1 (e.g. *pyrophyllite* and *talc*) or 1:1 type (e.g. *kaolinite*), surfaces which, although considered nonreactive due to the strong bonds between Si and O atoms, are predominantly hydrophobic and function as weak Lewis bases and can provide free electron pairs of surface oxygen for chemical bonds.
2. Sites related to isomorphous atomic substitution (e.g. Al per Mg or Si per Al), characterized by permanently negative electric charge and where the load deficit is compensated by the inorganic exchange cations (Ca, Mg, Na, K) or organic (being organic preferentially adsorbed compared to inorganic), sites that can occur in both the tetrahedral structural sheets and the octahedral structural sheets.
3. Sites of the structural interlayer spaces where cations of certain alkaline, alkaline-earth and transition metals when in the state of maximum oxidation (e.g. Cu^{2+} and Fe^{3+}, which being reduced can form organic cations) occupy exchange cationic sites.
4. Sites where water molecules envelop by solvation and coordinate the exchange cations becoming polarized and functioning as sources of Bronsted acidity yielding electrons.
5. Hydrophobic sites of the structural interlayer surfaces of the crystals of clayey minerals after the adsorption of organic molecules by these surfaces (e.g. when

alkylammonium cations replace inorganic cations in smectites, so-called organic clays, creating hydrophobic surfaces, serving the organic cations of molecular pillars that allow the adsorption and absorption of organic molecules).

6. Sites on the edges of lamellar crystals where broken links occur or where silanol and aluminol groups are exposed (either exposed structural groups or OH^- groups derived from the reaction of Si^{4+} and Al^{3+} ions not completely coordinated with water molecules and thus complete the respective coordinates).

Clay minerals acquire electric charge both in polar liquids such as water by two mechanisms:

1. First by atomic isomorphous substitutions both in tetrahedral and octahedral sheets, situations that create a permanent negative charge on the surfaces of clay mineral particles.
2. Second by broken -OH functional groups at the edges of the particles, the electric charge being dependent on water pH (at low pH values, -OH groups are protonated and acquire a positive charge, whereas at high pH values, they are deprotonated and acquire a negative charge).

But according to the same authors, clay minerals can acquire electric charge in non-aqueous apolar liquids by the addition of surfactants usually used to improve the stability of the mineral dispersion, the charging being the result of the acid-base mechanism of interaction between the clay particles and the suspending medium.

The location of the isomorphous, octahedral or tetrahedral substitution sites has a great influence on the adsorption of polar organic molecules. On the other hand, the OH groups of the crystalline edges of the clay minerals constitute strongly active sites and are responsible for the electric charge of pH-dependent clay and clayey soils. At low pH, the mentioned sites develop a positive charge due to the adsorption of protons and can interact with organic acids and oxyanions. Increasing the pH shows a certain value for which the electric charge is neutral (point of zero charge or PZC) and from this value the charge becomes negative. In clay minerals with very low electric charges, such as *kaolinite*, these pH-dependent sites are the main source of reactivity.

The very small particles of the clay minerals, because they present a greater number of crystallochemical defects, are those that present a greater number of active sites of the mentioned type, related to structural point defects (atomic isomorphous substitution and atomic omission), and other defects of planar and volumetric nature.

6.3.3 Basic Units of Clay Mineral Structures

The basic structural components of clay minerals, in increasing order of complexity, are the following: *ions*, *atomic planes* or *structural planes*, *structural sheets*, *structural layers* and *structural unit* (Fig. 6.2).

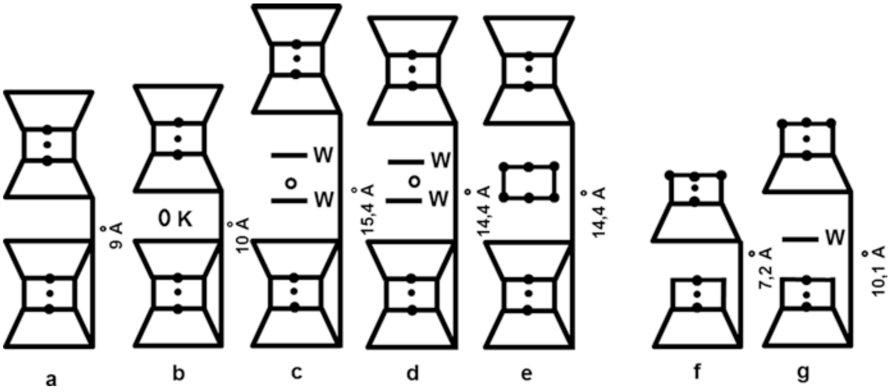
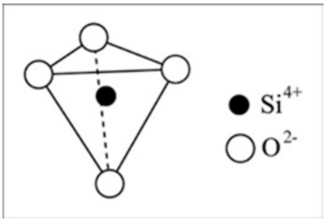


Fig. 6.2 Schematic representation of structures and respective basal spacings $d_{(001)}$ of the main clay mineral species: • octahedral cations; ◦ exchange cations; OH groups; 0 interlayer cations; w, water layers; (**a**) pyrophyllite; (**b**) mica; (**c**) montmorillonite; (**d**) vermiculite; (**e**) chlorite; (**f**) kaolinite; (**g**) fully hydrated halloysite

Fig. 6.3 Tetrahedron [SIO_4]



The *atomic planes* comprise the atoms on their ionic form that are arranged in the structure of the clay mineral. The *structural sheets* are groupings of atoms distributed through several atomic planes, atoms that constitute polyhedric configurations, *tetrahedron* or *octahedron* (Figs. 6.3 and 6.4), which in turn associate and form tetrahedral structural sheets and octahedral structural sheets (Figs. 6.5 and 6.6).

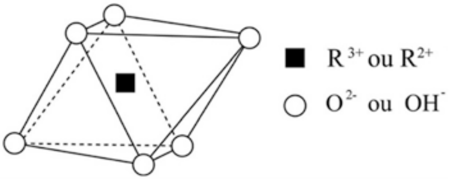
The basic building units of the clay mineral structures have configurations represented by tetrahedra in which the coordinating ion is Si^{4+} and the coordinated ion is O^{2-} and octahedra in which the coordinating ion is either Al^{3+} or Mg^{2+} and the ion coordinates are O^{2-} and HO^{1-}.

Both tetrahedral and octahedral units are linked together in planar developments, the so-called structural sheets – *tetrahedral sheet* (T) and *octahedral sheet* (O) – which in turn establish links between them, either through van der Waals bonds or through intercalation cations, and getting organized into the so-called structural layers.

The *structural layers* can be classified into three main types: T:O or 1:1, represented by the clay mineral *kaolinite*; T:O:T or 2:1, represented by the clay mineral *illite*; and T:O:T:O or 2:1:1, represented by the clay mineral *chlorite*.

The tetrahedral structural sheets have general composition T_2O_5, where T represents the tetrahedral cation, i.e. with 4 (four) or tetrahedral coordination. The

Fig. 6.4 Octahedron [(R^{2+} or R^{3+}) O_6], R^{3+} = Al, Fe^{3+}; R^{2+} = Mg, Fe^{2+}



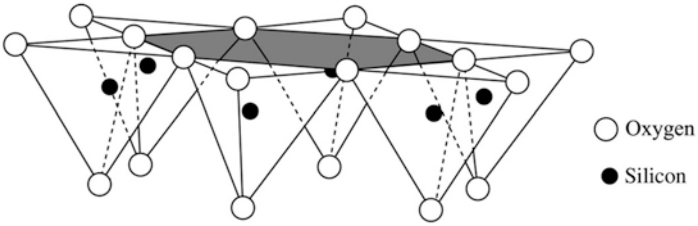


Fig. 6.5 Diagram of the tetrahedral structural sheet showing the hexagonal "hole" represented by the grey colour

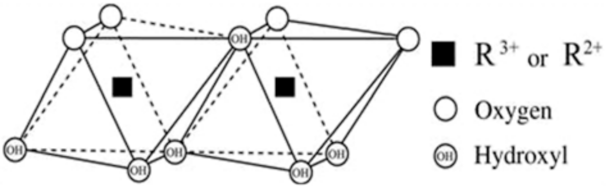


Fig. 6.6 Diagram of the octahedral structural sheet

tetrahedral cation which as a rule is Si can be partially replaced by Al and/or Fe. Also, Si occupies the tetrahedra centres, while the vertices are occupied by oxygens. Each tetrahedron connects to adjacent tetrahedra by sharing the three coplanar basal vertices occupied by oxygens, constituting the so-called tetrahedral structural sheet – the structural plane of the three basal oxygens is a two-dimensional hexagonal arrangement – while the fourth apex of each tetrahedron occupied by apical oxygen is part of the *octahedral structural sheet*.

In the octahedral structural sheets, the octahedra are connected laterally to each other, they have the respective centre occupied by an octahedral cation, that is, with 6 or octahedral coordination, and the octahedral cation can be Al^{3+}, Mg^{2+}, Fe^{3+} or Fe^{2+}, the six vertices of the octahedra being occupied by oxygens and/or hydroxyls. The *structural layers* are groupings of a number of structural tetrahedral and octahedral sheets and are the basic building blocks of the structures of the various clay minerals.

Finally, the *structural unit* is the basic motif that by symmetrical and periodic repetition originates the entire structure of the clayey mineral, which comprises the representation of the basic structural layer and the content of space, when there are structural interlayers. The *unit chemical formula* expresses the chemical composition of the *structural unit*. It is the organization of the *structural unit*, more precisely the number and nature of the structural tetrahedral (T) and octahedral (O) sheets, that make up the *structural unit*, and what determines the three basic structural types of clay minerals previously referred to: 1:1 or T:O; 2:1 or T:O:T; and 2:1:1 or T:O:T:O.

Figure 6.2 shows, schematically, the various structures and their respective characteristic basal spacings identified on X-ray diffraction patterns of the main clay mineral species.

The basal spacing $d_{(001)}$ of a 1:1 structure is slightly higher than 7 Å (angstrom) or 0.7 nm (nanometre), while the basal spacing $d_{(001)}$ of a 2:1 structure is about 10 Å, i.e. about 1 nm, and the basal spacing $d_{(001)}$ of a 2:1:1 structure is slightly higher than 14 Å, i.e. about 1.4 nm.

However, these basal spacings can deviate from the above values and take values between 7 Å and 18 Å depending on the type of the structural layer that is the basic component of the *structural unit* and the occupation of the structural interlayers by certain chemical species: cations, water and hydroxyls.

In the structural formula of a clay mineral, the global electric charge of the cations is compensated by the global electric charge of the anions. The latter, less affected by isomorphous atomic substitution, serve as the basis for calculations of crystallochemical formulas. Thus, for clay minerals with basal spacing values of 7 Å, 10 Å and 14 Å, the anionic loads corresponding to the half of the structural unit are as follows:

$$7\ \overset{\circ}{A} = O_5\left(OH\right)_4 = 14^{e-}$$

$$10\ \overset{\circ}{A} = O_{10}\left(OH\right)_2 = 22^{e-}$$

$$14\ \overset{\circ}{A} = O_{10}\left(OH\right)_8 = 28^{e-}$$

Figures 6.3 and 6.4 show the fundamental or basic units, tetrahedron and octahedron, the building blocks of clay mineral structures.

Each of these basic units, tetrahedron and octahedron, can be associated linking to adjacent tetrahedra and octahedra forming continuous two-dimensional patterns called tetrahedral and octahedral sheets, which in turn can be associated forming different three-dimensional layer organizations or structures of less or higher complexity, the clay mineral structures.

Table 6.3 Classification of *hydrous phyllosilicates* or *clay minerals* of planar structure (*In:* Guggenheim et al. 2006)

Layer type	Interlayer material[a]	Group	Octahedral character	Species[b]
1:1	None or H_2O only (x~0)	Serpentine-kaolin	Trioctahedral Dioctahedral Di,trioctahedral	Lizardite, berthierine, amesite, cronstedtite Kaolinite, dickite, nacrite, halloysite (planar) Odinite
2:1	None (x~0)	Talc-pyrophyllite	Trioctahedral Dioctahedral	Talc, willemseite, kerolite, pimelite Pyrophyllite, ferripyrophyllite
	Hydrated exchangeable cations (x~0.2–0.6)	Smectite	Trioctahedral Dioctahedral	Saponite, hectorite, sauconite, stevensite, swinefordite Montmorillonite, beidellite, nontronite, volkonskoite
	Hydrated exchangeable cations (x~ 0.6–0.9)	Vermiculite	Trioctahedral Dioctahedral	Trioctahedral vermiculite Dioctahedral vermiculite
	Hydrated mono- or divalent cations (x~ 0.6–0.85)	Interlayer-deficient mica	Trioctahedral Dioctahedral	Wonesite[c] None
	Non-hydrated monovalent cations (≥50% monovalent, x~ 0.85–1.0 for dioctahedral)	True (flexible) mica	Trioctahedral Dioctahedral	Phlogopite, siderophyllite, aspidolite Muscovite, celadonite, paragonite
	Non-hydrated divalent cations (≥50% divalent, x~1.8–2.0)	Brittle mica	Trioctahedral Dioctahedral	Clintonite, kinoshitalite, bityite, anandite Margarite, chernykhite
	Hydroxide sheet (x = variable)	Chlorite	Trioctahedral Dioctahedral Di,trioctahedral Tri,dioctahedral	Clinochlore, chamosite, pennantite, nimite, baileychlore Donbassite Cookeite, sudoite None
2:1	Regularly interstratified (x = variable)	Variable	Trioctahedral Dioctahedral	Corrensite, aliettite, hydrobiotite, kulkeite Rectorite, tosudite, brinrobertsite
1:1, 2:1			Trioctahedral	Dozyite

[a] x is the net layer charge per formula unit, given as a positive number

[b] Not an exhaustive list of species; in general, listed in order of abundance

[c] Net layer charge may be <0.6, but this is an exception

Table 6.4 Classification of *clay minerals*, hydrous phyllosilicates, of non-planar structure (*In*: Guggenheim et al. 2006)

Layer type	Modulated component	Linkage configuration	Unit layer, c sinβ value	Traditional affiliation	Species
Modulated structures					
1:1 Layer	Tetrahedral sheet	Strips Islands Other	7 Å 7 Å	Serpentine Serpentine None	Antigorite, bementite Greenalite, caryopilite, pyrosmalite, manganpyrosmalite, ferropyrosmalite, friedelite, megillite, shallerite None
2:1 Layer	Tetrahedral sheet	Strips Islands Other	9.5 Å 12.5 Å 9.6–12.5 Å 12.3 Å 14 Å	Talc Mica Mica/complex Other Chlorite	Minnesotaite Ganophyllite, eggletonite Zussmanite, caryopilite, manganopyrosmalite, ferropyrosmalite, friedelite, megillite, schallerite, nelenite Bannisterite Gonyerite
	Octahedral sheet	Strips	12.7–13.4 Å	Pyribole	Sepiolite, loughlinite, falcondoite, palygorskite, yofortierite
Rolled and spheroidal structures					
1:1 layer	None	Trioctahedral	-	Serpentine	Chrysotile, pecoraite
		Dioctahedral	-	Kaolin	Halloysite (non-planar)

6.3.4 *Crystallochemistry and Systematics of Clay Minerals*

Presently about 70 species of clay minerals are known, species distinguished by their crystallochemical specificities, which as a rule, based on common structural and chemical features, can be gathered into two main groups (see Tables 6.3 and 6.4, and Guggenheim et al. 2006):

1. *Planar hydrous phyllosilicates*, i.e. *planar clay minerals.*
2. *Non-planar hydrous phyllosilicates*, i.e. *non-planar clay minerals.*

Planar hydrous phyllosilicates comprise nine groups: *kaolin-serpentine*; *pyrophyllite-talc*; *smectite*; *true or flexible mica*; *interlayer-deficient mica*; *brittle mica*; *vermiculite*; *chlorite*; and *regularly interstratified* (*In:* Guggenheim et al. 2006).

All the groups referred to will be described below; those clay minerals with health interest and application, as are the cases of *kaolin* and *smectite*, deserved a more detailed treatment.

Non-planar phyllosilicates comprise clay mineral species whose particles exhibit fibrous, tubular and spheroidal shapes, and with these characteristics, two groups of clay minerals are defined: *halloysite*, *chrysotile*, *antigorite*, *sepiolite*, *palygorskite*, *allophane and imogolite*.

Sepiolite, *palygorskite* and *halloysite* due to their health interest and application deserved a more detailed treatment.

The underdescribed characterization of clay minerals gives particular development to those clay minerals recognized as having more interaction with human health.

6.3.4.1 Clay Minerals with Planar Structures

6.3.4.1a: Kaolin-Serpentine Group of Clay Minerals

Kaolinite and *halloysite* are dioctahedral T:O or 1:1 clay mineral, and they are the most representative species of the Al-rich *kaolin subgroup*, and their ideal chemical compositions are $Al_2Si_2O_5(OH)_4$ for *kaolinite* and $Al_2Si_2O_5(OH)_4.2H_2O$ for *halloysite*.

Dickite and *nacrite* are two other species of the *kaolinite subgroup*, really polytypes of kaolinite. Unlike *kaolinite*, *dickite* and *nacrite* whose particles exhibit platy shapes, *halloysite* particles can exhibit platy, tubular and spheroidal shapes.

Lizardite, *antigorite* and *chrysotile* are trioctahedral T:O or 1:1 clay mineral, and they are the most representative species of the *serpentine subgroup*, and being Mg rich, $Mg_3Si_2O_5(OH)_4$ is the expression of their ideal chemical composition.

Figures 6.5 and 6.6 schematically show the tetrahedral and octahedral sheets which are the basic components of the crystallochemical structures of the *kaolin-serpentine* group of clay minerals.

Figure 6.7 shows schematically the structure of the clay mineral *kaolinite*.

$R^{3+} = Al^{3+}$, Fe^{3+}… $R^{2+} = Mg^{2+}$, Fe^{2+}, Ni^{2+} …

In kaolinite, R^{3+} is aluminium Al^{3+}.

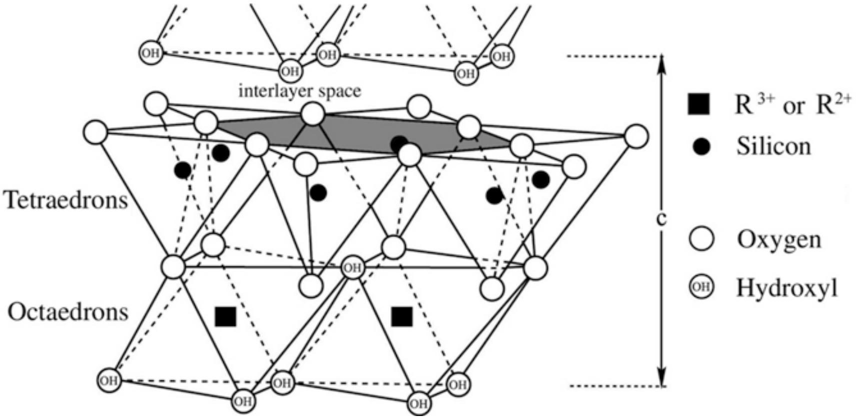


Fig. 6.7 Diagram of the T:O, OR TE:OC, OR 1:1 *kaolinite* structure

The name "kaolin" is derived from "Gaoling", the Chinese word meaning "High Ridge", a Chinese village near Jingdezhen in south-eastern China, Jiangxi Province. The name entered the English in 1727 from the French version of the word *kaolin*, following François Xavier d'Entrecolles's reports on the making of Jingdezhen porcelain.

Kaolinite subgroup minerals have a permanent dipole moment due to their structural asymmetry, the structural unit showing two distinct surfaces.

The theoretical chemical formula of *kaolinite*, structurally triclinic, is $Al_2Si_2O_5(OH)_4$, that means SiO_2-46, 54%; Al_2O_3-39, 50%; and structurally bonded hydroxyls, -13.96% (value corresponding to the weight loss on ignition).

The OH groups are very important constituents of the *kaolin subgroup minerals* (kaolinite, dickite and nacrite). There are two types of OH groups: structural OH coordinated to Al and surface OH positioned at the layer broken edges. The structural OH groups through hydrogen bonds OH…O condition the layer stacking.

A typical crystal of kaolinite has a thickness of the order of 50 to 100 nm, the thickness of a single kaolinite structural layer being 0.7 nm, which means that the typical crystal before referred to consists of 70–200 individual layers stacked on top of each other Layers are stacked along the c axis by hydrogen bonding interaction. The electrical charge of the layer unit is near to zero.

Exposed surface OH groups, especially under-coordinated OH groups positioned at the broken edges, exert great influence on clays' rheological properties as well as on their ability to bind metals and oxyanions. Water molecules are always associated with clay minerals due to the small particle size, large external and internal surface area and electric charge of clay minerals.

Intercalation of certain polar molecules (e.g. K-acetate, urea, hydrazine, dimethyl sulphoxide and formamide) in *kaolinite* interlayer spaces is an important property of *kaolinite*, and it can take place when the bonding energy of the intercalate compound overcomes the original interlayer energy. The molecules referred to have the ability to interact favourably with both the siloxane and surface hydroxyls and to overcome the existing interlayer forces. Although direct intercalation is limited to small intercalate molecules, larger molecules can be introduced indirectly into the interlayer space following the formation of "primary intercalates" (Johnston 2010).

Chemical intercalation associated to ultrasonication can be used for kaolinite delamination, important for certain kaolinite applications. Kaolinite delamination can be achieved by grinding and high-pressure extrusion. In *kaolinite*, the bonding between adjacent structural layers is made through hydrogen H–O bonds and van der Waals bonds, naturally weak chemical bonds, reason why *exfoliation* in kaolinite as well as in other *kaolin minerals* requires low energy. In *kaolinite*, the interlayer space (Fig. 6.7) is almost inexistent.

Kaolinite normally occurs as stacked pseudohexagonal platelets frequently exhibiting booklet-like shape (Fig. 6.8). Each *kaolinite platelet* is an association of several structural layers, each layer consisting of one tetrahedral sheet bond to one octahedral sheet.

Like in other clay minerals, structural order-disorder occurs in kaolin subgroup minerals. For instance, various order-disorder degrees can be found in kaolinite,

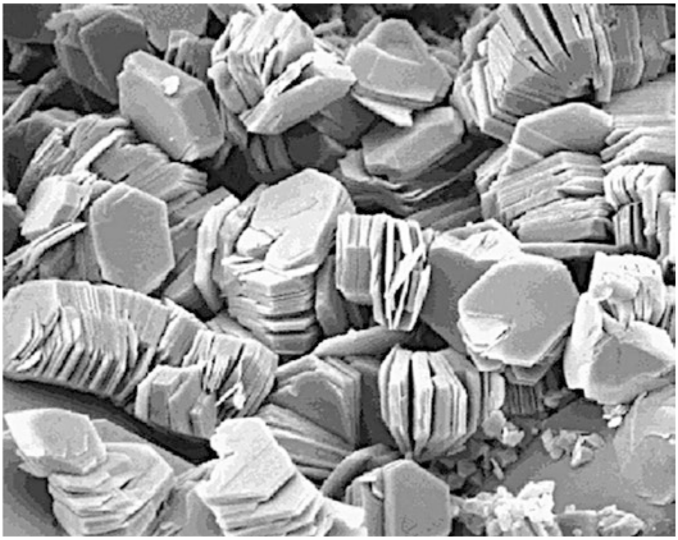


Fig. 6.8 "Booklets" of pseudohexagonal platy particles of *kaolinite*

which can condition, for instance, rheological properties and chemical activity (Plançon and Thchoubar 1977a, b; Plançon 2001; Johnston et al. 2008).

Kaolinite is very resistant to chemicals (chemical inertness over a wide range of pH 4–9) and to heat (melting point at 1785 °C). In raw kaolin, *kaolinite* is associated to minerals considered as impurities such as *quartz*, *feldspar*, *mica*, *anatase*, *rutile* and iron oxides and hydroxides (*hematite*, *goethite*).

Each *kaolinite layer* is considered a strong dipole: the *siloxane surface* being hydrophobic is dominated by negative charges; the *aluminol surface* being hydrophilic is dominated by positive charges. Such explains why *kaolinite* individual layers are strongly bonded by hydrogen and dipolar interactions.

Kaolin and kaolinite are classified as eco-friendly mineral resources with important applications in biomedicine, energy and electronics. Most applications require the modification and transformation of kaolinite crystallochemistry, through thermal activation, acid activation, alkaline activation, mechanical activation and organification activation.

A reference is due to a very recent work of Cheng et al. (2019) on "Kaolinite Nanomaterials: Preparation, Properties and Functional Applications" that is Chap. 6 of the book entitled *Nanomaterials from Clay Minerals: A New Approach to Green Functional Materials* edited by Wang A and Wang W and issued by Elsevier. The main reserves of kaolin and kaolinite occur in the USA, Brazil, England, France, Germany and China.

There are clay minerals of the *kaolin group* which particles do not show platy morphology; indeed, they commonly exhibit tubular shapes and rarely spherical shapes.

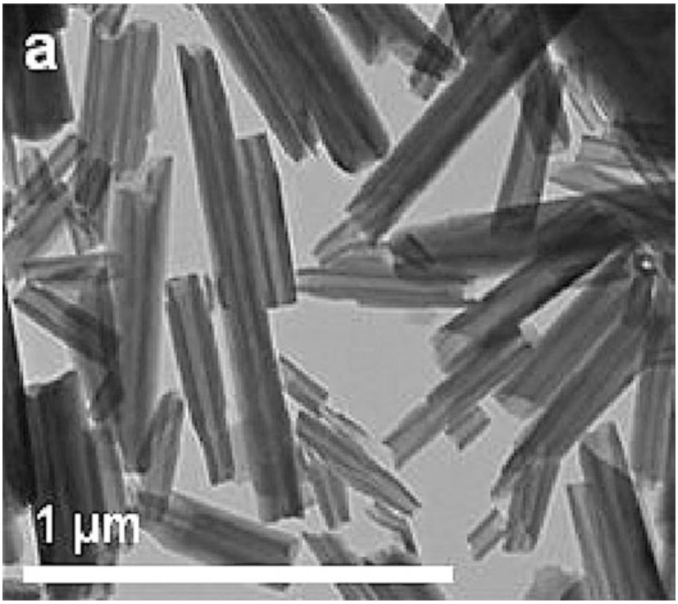


Fig. 6.9 Rolled and tubular particles of *halloysite*

Figure 6.9 shows the tubular shape that, as a rule, is exhibited by *halloysite* crystals, *halloysite* being a species that belongs to the *kaolin subgroup* of clay minerals characterized by dioctahedral T:O structures.

The name *halloysite* was dedicated by Berthier in 1826 to Baron Omalius d'Halloy who investigated this mineral found in dissolution cavities of Carboniferous limestone, in the region of Liège, Belgium. *Halloysite* may be considered as being a *hydrated kaolinite*, water being present in the interlayer space, hence justifying the general chemical formula $Al_2Si_2O_5(OH)_4.2H_2O$, characterized by a layer periodicity of 10 Å, i.e. $d_{(100)} = 10$ Å. Comparatively to *kaolinite* which $d_{(100)} = 7.2$ Å, *halloysite* has an additional water monolayer between the adjacent layers.

Brigatti et al. (2006, 2013) and Detellier and Schoonheydt (2014) propose explanations for the change of *kaolinite* platelets into *halloysite* rolls. The substitution of Fe^{3+} for Al^{3+}, the first larger than the second, the distribution of vacant sites in the octahedral sheet and the orientation of hydroxyl groups could contribute for that change. *Halloysite rolls* or *tubes* are formed as a result of strains caused by lattice mismatch between adjacent tetrahedral and octahedral sheets.

Hydrated halloysite has a layer periodicity or basal spacing very close to 10 Å, reason why it is called *halloysite 10 Å*. The interlayer water can be easily removed at 70–100 °C, and the dehydrated form having a basal spacing of 7.2 Å is called *halloysite 7 Å*, although the name *metahalloysite* is sometimes used.

According to Churchman et al. (1972), the dehydration process is progressive. Natural *halloysite* may exhibit intermediate degrees or levels of hydration.

The collapse of the *halloysite* structure occurs at approximately 400 °C, i.e. at lower temperature than the one required for kaolinite structure collapse.

Pure kaolinite and halloysite are white minerals. In case they exhibit other colours (yellowish to brown), such is due to isomorphous substitution of Si^{4+} or Al^{3+} by metal ions, such as Fe^{3+}, Cr^{3+} and Ti^{4+}.

Differences in ion size and other structural defects (e.g. ion vacancies) may cause the weakening of the interlayer hydrogen bonds and consequently the rolling of the multilayer *halloysite* structure. The mechanism of halloysite curling is still a matter of discussion. Kirkman (1981) has proposed a curling mechanism based on crystal internal dislocations. Dimensions of the *halloysite* tubes vary depending on the natural occurrence, the tubes length in the range of 0.5–2.0 μm, the outside diameter in the range of 50–200 nm and the internal lumen diameter in the range of 10–50 nm.

One of the important features of *halloysite* tubes is the different surface chemistry of the inner and outer sides of the tubes: silica sheets occur on the external surfaces of the tubes and exhibit a negative charge above pH 1.5, whereas alumina sheets make up the inner surfaces involving tubes lumen showing a positive charge up to pH 8.5. The difference in tubes surface charges allows for the selective modification of inner and external surfaces of *halloysite nanotubes* and selective loading of negatively charged molecules within halloysite internal lumens.

Halloysite nanotubes can be selectively modified at external or internal sides by using silanes or polyphosphates. *Halloysite nanotubes* can be loaded with a broad variety of substances, from simple organic and inorganic molecules to high-molecular-weight polymers and biologically active substances, including drugs and enzymes (Price et al. 2001; Lvov et al. 2008; Lvov 2008; Levis and Deasy 2003; Kelly et al. 2004).

Churchman and Pasbakhsh (2015) discuss the current trends in research and application of natural mineral nanotubes. *Halloysite* nanotubes can be successfully loaded with various types of active agents including pharmaceutical agents and antibacterials. Lumen loading capability and controlled release are important features in what concerns biomedical applications. The release from halloysite lumen could last from several hours to days depending on molecular mass, structure and solubility of the active agent in the release medium (Lvov and Abdullayev 2013; Abdullayev and Lvov 2013).

A significant number of studies involving active agents encapsulated by halloysite nanotubes have been reported, such as *ibuprofen*, *curcumin*, *resveratrol*, *ofloxacin*, *gentamicin* and *mercaptobenzothiazole*.

Only two high-grade *halloysite* deposits are known in the world: one in Northland, New Zealand, from weathered rhyolite, and the other in the Tintic district of Utah, USA.

Wilson and Keeling (2016) describe the characteristics of most known commercial, or potentially commercial, *halloysite* deposits, in terms of both their geological settings, and also some of the main commercially important properties of the *halloysites* being mined, properties which include purity, composition, shape, colour and associated minerals. Hillier et al. (2016) describe systematic relationships between features in their X-ray diffraction patterns and infrared spectra that reflect variations in the size, shape and other physical characteristics of the halloysite nanotubes (HNTs).

Not all halloysites exhibit particle tubular shape. Cunningham et al. (2016) describe the novel occurrence in vermicular "book" form of *halloysite* in tuffs from New Zealand. The authors propose a mechanism for their formation that involves transformations from spherical, tubular and also platy forms.

Spheroidal or onion-like morphology of *halloysite* crystals is much rare than the tubular morphology, but in general they can coexist in the same deposit, situation recently well exemplified in *halloysite* deposits from Rio Negro, Patagonia, Argentina (Cravero et al. 2016), in which *halloysite*/*kaolinite* concentration ratio ranges from 75–25 to 100–0, *halloysite* and *kaolinite* being formed from weathering of volcanic-pyroclastic rocks.

The formation process of *spheroidal halloysite* is still a matter of discussion. Some authors consider that *spheroidal halloysite* results from the fast dissolution of volcanic glass yielding supersaturated solutions which favour the formation of this particular shape (Quantin et al. 1988; Adamo et al. 2001; Churchman et al. 2016).

The medicinal interest of *tubular halloysite* has only raised after 2005, in particular as drug carrier.

Recently, Hanif et al. (2016) have reviewed HNTs as a delivery system with applications in anticancer therapy, sustained and controlled release drug delivery systems, cosmetics, delivery of proteins, vaccines and genes. The authors have identified some characteristics of HNTs that are relevant to their use in these applications along with some of the methods for loading the tubes.

The use of *tubular halloysite* as drug carrier and deliver will be dealt with in Chap. 10 of this book. Unlike *tubular halloysite*, no medical applications have been found for *spheroidal halloysite*.

Some other authors propose that the origin of *spheroidal halloysite* is related to transformation of *allophane* (Askenasy et al. 1973; Sudo and Yotsumoto 1977; Quantin et al. 1988; Adamo et al. 2001).

6.3.4.1b: Pyrophyllite-Talc Group of Clay Minerals

There are clay minerals which structures are based on T:O:T or 2:1 structural layer, an octahedral sheet sandwiched by two tetrahedral sheets. There are clay minerals exhibiting such structure and simple chemical composition; they form the *pyrophyllite*/*talc group*, *pyrophyllite* $Al_2Si_4O_{10}(OH)_2$ being the dioctahedral species and *talc* $Mg_3Si_4O_{10}(OH)_2$ being the trioctahedral species.

The ideal structural layers of *pyrophyllite* and *talc* are nearly electrically neutral, and then no charge-balancing cation is present in the interlayer space. Isomorphous atomic substitutions are very limited, of Al^{3+} for Si^{4+} in *pyrophyllite* and of Al^{3+} or Fe^{3+} for Mg^{2+} in *talc*. Therefore, contiguous layers are held together mainly by van der Waals bonds, reason why crystal exfoliation requires very low energy.

Dehydration, that is, the loss of hydroxylic water, occurs in *pyrophyllite* above 800 °C. Talc-like minerals are *kerolite* (hydrated variety), *minnesotaite* (Fe-rich variety) and *willemesite* (Ni-rich variety). According to Harvey and Lagaly (2013), *talc* and *pyrophyllite* are important filler materials for polymer and rubber.

Talc is also used extensively in cosmetic and pharmaceutical powders. Talc is the softest known mineral. *Talcum powder* is made of pulverized talc. When it is finely ground, talc creates a smooth and silky powder that absorbs moisture, reduces odours and cuts down on friction. Those properties make it an ideal ingredient in baby powder, deodorant, makeup and hundreds of other consumer products. Talc dust can cause significant harm if it is swallowed or inhaled. Current research indicates that pure talc does not cause mesothelioma. However, if talc is contaminated with *asbestos* and *asbestiform minerals*, it could lead to the development of *mesothelioma*.

6.3.4.1c: True or Flexible Mica Group of Clay Minerals

There are clay minerals still based on T:O:T or 2:1 layer characterized by more complex chemical composition; they form the *group of true or flexible mica*, the *group of brittle mica*, the *group of interlayer-deficient mica*, the *group of smectite*, the *group of vermiculite* and the *group of chlorite*, all having in common a similar structural model. In each of these groups, there are dioctahedral and trioctahedral species.

The *group of true* or *flexible mica* and the *group of brittle mica* are distinguished from the *group of smectites* just in the interlayer space. Unlike the second group of clay minerals, the first group of clay minerals has non-hydrated exchangeable cations in the interlayer space.

True or *flexible mica* is distinguished from *brittle mica* because the interlayer of *true mica* is occupied by non-hydrated monovalent cations such as K^+ or Na^+ and the electric charge is x~0.85–1.0, whereas the interlayer space of *brittle mica* second is occupied by non-hydrated divalent cations such as Ca^{2+} and the electric charge is x~1.8–2.0.

Three representative species of *true* or *flexible mica* are identified and expressed by their structural chemical formula as follows:

Muscovite, $KAl_2(Si_3,Al)O_{10}(OH)_4$, known as white mica, is K and Al rich and dioctahedral true mica most widespread in the Earth's crust.

Biotite, $(K_{0.78}Na_{0.16})(Mg_{1.68}Fe^{2+}{}_{0.71}Fe^{3+}{}_{0.19}Ti_{0.34}Al_{0.19}Mn_{0.01})Si_{2.86}Al_{1.14})O_{10}(OH_{0.71}F_{0.29})$, known as black mica, is Mg and Fe rich and trioctahedral true mica most widespread in the Earth's crust.

Phlogopite, $(K_{0.93}Na_{0.04}Ca_{0.03})(Mg_{2.77}Fe_{0.10}Ti_{0.11})(Si_{2.88}Al_{1.12})O_{10}(OH_{1.49}F_{0.51})$, is the magnesium end member of the biotite solid solution series.

6.3.4.1d: Brittle Mica Group of Clay Minerals

Margarite, $CaAl_2(Al_2Si_2)O_{10}(OH)_2$, is the dioctahedral species, and *clintonite*, $Ca(Mg_2Al)(Al_3Si)O_{10}(OH)_2$, is the trioctahedral species, both the most representatives of *brittle micas*. The detailed classification of the mica group has been proposed by Rieder et al. (1998).

6.3.4.1e: Interlayer-Deficient Mica-Like Group of Clay Minerals

Illites, known as clayey micas, are the most abundant clay minerals in the Earth's crust, continental and marine. *Illite* is a dioctahedral interlayer-deficient series name to describe certain micas after only optical microscopic data become available.

Other dioctahedral interlayer-deficient micas of a series type are *glauconite* and *brammallite*.

There are *dioctahedral illite* and *trioctahedral illite*, the first crystallochemically close to *muscovite*, the second crystallochemically close to *biotite*, differentiated by much smaller crystal size, more degraded structure, little less Al content in the octahedral sheet, little less K content and little higher H_2O content in the interlayer space.

According to Brigatti and Guggenheim (2002), the term *illite* is applied to very fine 2:1 clay mineral which shows a non-expandable layer and a wide variety of chemical compositions.

Figure 6.10 shows the crystallochemical features of *illite/mica* (Grim 1962).

The chemical composition of *illite* differs from the composition of muscovite in having heterovalent isomorphous substitution (Al^{3+} for Si^{4+} and Fe^{2+}, Mg^{2+} for Al^{3+}) as well as homovalent isomorphous substitution (Fe^{3+} for Al^{3+}) and a layer charge between 0.6 and 0.9.

The diffraction maxima, on the X-ray diffraction patterns, are not as sharp in *illite* as in *muscovite*. Unlike in most of 1:1 clay mineral represented by *kaolinite*, in 2:1 clay mineral, the interlayer space between structural layers exists with a fixed value in micas and illite and with a variable value in *smectites* dependent upon the solvation capacity of the interlayer cation, Na^+ or Mg^{2+}.

In smectites, the nature of the interlayer cation very much conditions the smectites swelling capacity, highly dependent on the atomic substitution that mainly occurs in the inner octahedral structural sheets. Swelling is justified by the weak electrostatic energy existent between adjacent structural layers. Unlike in *smectites*, in *micas* and *illites*, the atomic substitution mainly occurs in tetrahedral sheets, i.e. in the outer sheets of the structural layers, reason why it is high the electrostatic energy of the bonds between adjacent structural layers.

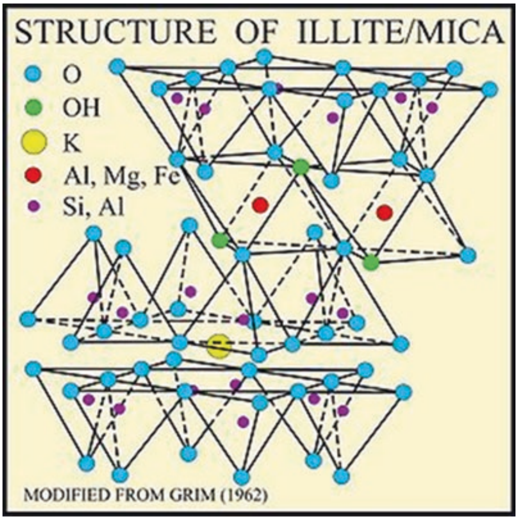


Fig. 6.10 Schematic representation of *illite/mica* structure

Within clay minerals, *illite* is the most common in the Earth's crust, being the major constituent of shales. In geological studies, illite "crystallinity" is a crystallochemical parameter used to classify low-grade metamorphic activity in pelitic rocks (Abad 2003). Determining the "illite crystallinity index" allows geologists to designate what metamorphic facies and metamorphic zone the rock was formed in and to infer what temperature the rock was formed.

According to Merriman and Peacor (1998) three kinds of data are useful to deduce the sedimentary-basin maturity what is of paramount importance, for instance, to determine the hydrocarbon potential of a sedimentary basin:

1. Clay mineral assemblages
2. Quantification of mixed-layer clay minerals
3. Clay minerals "crystallinity"

The Kübler index (KI) introduced by Kübler (1964) for petroleum exploration purposes is the preferred index to be used in illite crystallinity studies based on its reproducibility and simplicity. The KI measures the changes in the shape of the first X-ray diffraction basal reflection (d_{100}) of illite-muscovite that corresponds to a spacing of approximately 10 Å and is experimentally determined by measuring the full width at half maximum height.

Prior to the introduction of the Kübler index, there were two other indices used to classify illite crystallinity in low-grade metamorphic rocks: Weaver index and Weber index. The KI is a valid tool, successfully applied to many fine-clastic metasedimentary sequences to detect the anchizonal limits in sedimentary basins and in the outer fold-and-thrust zones of orogenic belts.

6.3.4.1f: Smectite Group of Clay Minerals

Smectite group of clay minerals are 2:1 hydrous phyllosilicates with a total negative layer charge between 0.2 and 0.6 per *formula unit* (FU) or half *unit cell* (UC).

Except for the layer charge and hydration of the interlayer cations, smectite structure is similar to that of other 2:1 hydrous phyllosilicates already described.

The octahedral sheet may be dominantly occupied either by trivalent cations e.g. Al(III) or FE(III), in the case of *dioctahedral smectites* or by divalent cations e.g. Mg(II), in the case of *trioctahedral smectites*. *Dioctahedral* and *trioctahedral smectites* are two subgroups of the *smectite group of clay minerals*.

Commonly Si^{4+}, Al^{3+} and Fe^{3+} occupy the tetrahedral sites, and substitution of Al^{3+} and/or Fe^{3+} for Si^{4+} creates an excess of negative charge on the three basal oxygens and the apical oxygen affecting the total layer charge as well as the local negative charge at the layer surface. Commonly too, Al^{3+}, Fe^{3+}, Fe^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+} and Li^{+} occupy the octahedral sites. The negative electrical charge of the layers is balanced by hydrated exchangeable cations, mostly Ca^{2+}, Mg^{2+} and Na^{+} located in the interlayers spaces.

In *dioctahedral smectites* (*montmorillonite*, *beidellite*, *nontronite* and *volkonskoite*), substitution of divalent cations for trivalent cations creates an excess of negative layer charge, whereas substitution of trivalent cations for divalent cations in *trioctahedral smectites* (*hectorite*, *saponite*, *sauconite*, *stevensite* and *saponite*) creates an excess of positive charge, and such events have implications on physical properties of smectites, such as swelling and rheological behaviour.

As aforesaid, the *montmorillonite* chemical formula can be expressed as follows: $(Na,Ca)_{0.33}(Al,Mg)_2(Si_4O_{10})(OH)_2\ nH_2O$.

Montmorillonite was first described in 1847, and it is named after Montmorillon, a commune in the Vienne Department in the Nouvelle-Aquitaine region in western France, where the reference occurrence was found. Uddin (2017) provides an overview on *montmorillonite* structure, functional properties and applications.

In *beidellite*, Al^{3+} is the major octahedral cation; in *nontronite*, Fe^{3+} is the major octahedral cation; and in *volkonskoite*, Cr^{3+} is the major octahedral cation.

The interlayer space or thickness of *smectite* is variable depending upon the nature of the interlayer cation and of the humidity or moisture of the environment where it stays, reason why *smectites* are classified as *expansive* or *swelling clay minerals* (Fig. 6.11).

Emiel and Hensen (2002) discuss the mechanism that causes clay swelling. Swelling proceeds by the migration of counterions initially strongly bound to the clay mineral surface to positions in the clay mineral interlayer where these ions are fully hydrated. *Montmorillonite* swelling is dependent on charge locus (mostly on the octahedral sheet or mostly in the tetrahedral sheet), charge density and the type of counterion.

Most of *smectite* minerals applications are related to reactions that take place in the interlayer space. Na^+, K^+, Ca^{2+} and Mg^{2+} that balance the negative layer charge are commonly hydrated and exchangeable.

According to Emmerich (2013), the amount and location of layer charge, both in tetrahedral and octahedral sheets, together with the kind of interlayer cations, strongly influence both physical and chemical properties of smectites.

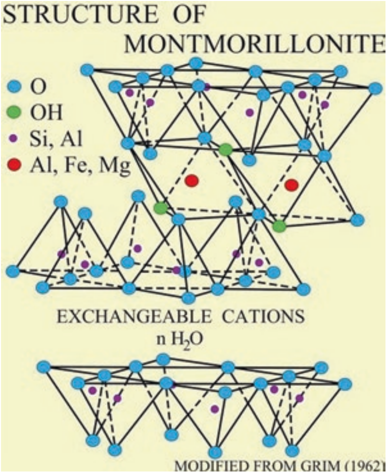


Fig. 6.11 Schematic representation of the crystalline structure of *montmorillonite*

Smectites contain water in several forms: structural, zeolitic and free water. *Smectite species* may be differentiated by the following criteria, particularly proposed by Emmerich (2009):

1. Overall chemical composition with particular attention to the content of elements other than Si, Al and Mg.
2. Dioctahedral or trioctahedral nature of the octahedral sheet.
3. Predominant octahedral cation.
4. Cation distribution within the octahedral sheet of dioctahedral smectites, that is, *cis* and *trans* positions.
5. Density and location of the layer charge.

Sodium montmorillonite, *calcium montmorillonite* and *hectorite* are the most industrially used *smectites* both in pharmacy and medicine. *Sodium montmorillonite* and *hectorite* have high base-exchange capacities, generally within the range of 80–130 meq/100 g.

Calcium montmorillonite, on the other hand, has a base-exchange capacity within the range of 40–70 meq/100 g.

In pharmacopoeias, the term *bentonite* is used to refer to a natural, colloidal, hydrated aluminium silicate (Viseras et al. 2006).

Gelwhite® N-NF, Bentolite® MB-NF, Mineral Colloid® BP and Mineral Colloid® MO are *bentonite* trade names. The clay mixtures of *montmorillonite* and *saponite* are known by the trade names Veegum®, Gelwhite® MAS, Gelsorb®, Carrisorb®, Pharmasorb Regular® and Bentopharm®. When the clay is only constituted by *montmorillonite*, it is known as purified bentonite, and its trade name is Veegum® HS (Viseras et al. 2007). To all the trade names referred to correspond a data sheet containing the product description, properties and applications.

Bentonite is a type of clay in which the clay mineral *montmorillonite* is the essential constituent and whose name goes back to the American geologist Knight. Around the year 1890, he explored in Wyoming (USA) near Fort Benton a clay deposit. After the place of discovery, this material was named *bentonite*.

Colloidal rheological and absorption properties justify the wide range of *bentonite* applications in the pharmaceutical industry (Carretero et al. 2013; Modabberi et al. 2015) and in *pelotherapy* and *medicine* (Karakaya et al. 2010; Carretero et al. 2010, 2013; Gomes et al. 2013a, b; Gomes 2018).

Especially in pharmaceutical and cosmetic formulations, *bentonite* must comply with restrictive chemical, physical, microbiological and toxicological requirements (Viseras et al. 2006; López-Galindo et al. 2007). *Smectite clays* have been used as support materials in drug slow-release systems.

The higher layer charge of *sodium montmorillonite* and *hectorite* makes possible the exchange of hydrated cations by polar organic molecules such as ethylene glycol, quaternary amine and polyalcohols. This important property is used in very useful products, the so-called organoclays.

Smectite clay mineral surfaces generally show selectivity for organic cations and protonated organic bases. Sorption of nonpolar or weakly polar organic molecules in the interlayer spaces can occur if the clay mineral is not highly hydrophilic. In the last two decades, the use of clay-organic interactions has rapidly expanding, with important technological applications, some in the human health field.

Because of the high specific surface, high layer charge and base-exchange capacity, *sodium montmorillonite* has a high swelling capacity of the order of 10–15 times when placed into water. *Calcium montmorillonite* has a much lower swelling index, 2–3.

Diosmectite is the trade name of a type of *calcium montmorillonite* valued in medicine for its antidiarrhoeal effects justified for its strong adsorbent properties, so it is used as an intestinal adsorbent in the treatment of several gastrointestinal diseases, including diarrhoea.

Montmorillonite clay mineral has proven to be effective against *Candida albicans*, a type of fungus which is a causal agent of opportunistic oral and genital infections known as *candidiasis*.

Very recently, Zhou et al. (2019) produced an interesting article entitled "Smectite Nanomaterials: Preparation, Properties and Functional Applications" that is Chap. 7 of a book of 13 chapters entitled *Nanomaterials from Clay Minerals: A New Approach to Green Functional Materials*, with Wang A and Wang W (editors), published by Elsevier. This article is an update overview on smectite clay minerals in what concerns their natural and modified properties, as well as the various functional applications. The authors enhance the applied interest of the modifications that can be promoted both on surfaces and interlayer spaces of montmorillonite crystals. For instance, the interlayer spaces of montmorillonite crystals can be intercalated with guest cations through an ion-exchange reaction or other physical and chemical interactions in order to yield organo-montmorillonite, and this can be exfoliated or delaminated into thin nanolayers for producing clay-polymer nanocomposites able to exhibit improved barrier, mechanical strength, thermal stability and fire retardant properties.

Hectorite is a rare natural white or near white clay mineral species belonging to the subgroup of trioctahedral smectites, and it is characterized by the chemical formula $Na_{0.3}(Mg,Li)_3Si_4O_{10}(OH,F)_2$ and is well represented in an occurrence located near Hector, in San Bernardino County, California, USA, where it is associated with bentonite as an alteration product of the zeolite *clinoptilolite* in a deposit of volcanic ash and tuff with high glass content. *Hectorite* is important in the cosmetics industry, used as suspending agent and rheology modifier due to the specificities of its particle size, shape and charge. Hectatone™ is an organoclay based on *hectorite*.

Bentone® MA is a rheological additive based on purified *hectorite* clay that imparts thixotropy and good anti-settling to water-based cosmetic systems.

There is enough experience on the synthesis of certain clay minerals which applications require consistent properties that could not be provided by natural minerals (Zhang et al. 2010; Jaber et al. 2013).

Laponite is a synthetic trioctahedral smectite clay mineral with a hectorite-like composition, $Na_{0.7}Si_8Mg_{5.5}Li_{0.3}O_{20}(OH)_4$. However, very recently, Christidis et al. (2018) have questioned if *laponite* is pure hectorite or a mixture of different trioctahedral phases.

Saponite is a trioctahedral smectite, a clay mineral of chemical composition $(Na,Ca)_{0.3}(Mg,Fe)_3(Si_{4-x},Al_x)_4O_{10}(OH)_2 4H_2O$, and was first described in 1840 in the occurrence type, in Lizard Point, Landewednack, Cornwall, England, UK. The name *saponite* is derived from the Greek word *sapo*, meaning soap.

The saponiferous clay with trade name Ghassoul or Rhassoul is produced in Morocco and commercialized by the Societé du Ghassoul et de ses derivés, SARL, Quartier Industriel de Sidi Brahim, Fes, Morocco. The name *ghassoul* signifies washing and cleaning, and *ghassoul clay* showing brown and beige colour and characterized by high water absorption power (15 g of *ghassoul* absorbs 25 g of water) and high cation exchange capacity (75 meq/100 g) is classified by the producer as a smectitic clay mainly constituted by lithium *stevensite*.

Stevensite is one Mg-rich (around 25% of MgO) trioctahedral smectite clay mineral.

6.3.4.1g Vermiculite Group of Clay Minerals

Vermiculite group of clay minerals comprises dioctahedral and trioctahedral species. As in *smectite* minerals, the 2:1 *vermiculite* structural layers are separated by hydrated cations occupying the interlayer space. However, the negative layer charge of *vermiculite* (>0.6 per formula unit), which arises mostly from substitution of Al^{3+} for Si^{4+} in tetrahedral sites, is larger than that of smectite.

Vermiculite group of clay minerals comprises dioctahedral and trioctahedral species. As in smectite minerals and in trioctahedral micas, the *vermiculite* 2:1 structural layers are separated by hydrated cations, as is the case of Mg^{2+}, occupying the interlayer space.

The water molecules solvating Mg^{2+} ions are structured in two planes. However, the negative layer charge of *vermiculite* (>0.6 per formula unit), which arises mostly from substitution of Al^{3+} for Si^{4+} in tetrahedral sites, is larger than the negative layer charge of smectite, reason why the expansion or swelling of *vermiculite* is more limited than the expansion of *smectite* that is characterized by lower electric charge (0.2–0.6).

The chemical composition of *vermiculite* can be expressed as $E^+(Mg^{2+}, Fe^{2+}, Fe^{3+}, Al^{3+})_6(Si,Al)_8O_{20}(OH)_4nH_2O$, where E^+ represents the exchange cation, commonly Mg.

The *vermiculite* occurring in clays is characterized by a basal spacing d_{100} of ~14 Å that do not totally collapse to ~10 Å, as happens with smectites when heated to ~300 °C after saturation with K, and do not expand totally as *smectites* do.

The name of the group is derived from the name *vermiculite* of the macroscopic species which crystals look like worms, vermiculus in Latin, crystal shape acquired after heating.

No pharmaceutical and medical applications are known for *vermiculite*. Vermiculites are commonly used in the form of expanded particles by rapid heating from 250 °C to 1500 °C followed by immediate cooling to 400 °C.

The evaporating water expands vermiculite particles in worm-like (vermiform) manner (Grim 1968; Bergaya et al. 2006) increasing its volume by up to 1500 times.

Expanded vermiculite is used in the building industry for heat insulation and sound dissipation (Harvey and Lagaly 2013).

6.3.4.1h: Chlorite Group of Clay Minerals

Chlorite group of clay minerals crystallochemically differ from the trioctahedral micas due to the existence of one octahedral sheet, a brucite-like sheet, positioned between the T:O:T mica layers. As a matter of fact, the *chlorite* layer structure can be expressed by T:O:T:O or 2:1:1 and is characterized by a basal spacing d_{100} of ~14 Å or 1.4 nm.

Chlorite ideal chemical composition is shown as $(Mg,Fe)_3(Si,Al)_4O_{10}(OH)_2$. The brucite-like sheet occupying the interlayer position has the general composition $(Mg,Al)_3(OH)_6$. There is quite a range of cation substitution in *chlorites*, most commonly Mg^{2+}, Fe^{2+}, Al^{3+} and Fe^{3+}.

Bonding between adjacent *chlorite* structural layers is made by hydrated or solvated ions of Mg, Al, Fe or Li.

There are dioctahedral, trioctahedral (the most frequent with Mg^{2+}, Al^{3+}, Fe^{3+} and Fe^{2+} on octahedral sites), di-trioctahedral and tri-dioctahedral *chlorites* (Bailey 1980a, b). Tetrahedral cations are Si^{4+} and Al^{3+}. Occasionally, other cations different from those referred to can replace the normal ones.

Within trioctahedral chlorites, *clinochlore* (the Mg end member), *chamosite* (the Fe end member) and *pennantite* (the Mn end member) are the most common. *Donbassite* is an Al-rich dioctahedral chlorite; *sudoite* is a di-trioctahedral Al- and Mg-rich chlorite; *cookeite* is a di-trioctahedral Li- and Al-rich chlorite.

Di-trioctahedral chlorites, such as sudoite and *cookeite*, have a dioctahedral layer and a trioctahedral interlayer. There are no known tri-dioctahedral chlorite structures. The name chlorite is derived from the Greek name *chloros*, meaning pale green, a colour commonly exhibited by macroscopic *chlorite*. *Chlorite* is commonly found in shales and also in underclays associated with coal seams.

No pharmaceutical and medical applications are known so far for *chlorite*.

6.3.4.1i: Regular and Irregular Interstratified Planar Clay Minerals

In addition to the clay minerals or better to the clay mineral species referred to in subtopics 6.3.4.1a, 6.3.4.1b, 6.3.4.1c, 6.3.4.1d, 6.3.4.1e, 6.3.4.1f, 6.3.4.1g and 6.3.4.1h, there are still some clay minerals with a 2:1 planar structure which exhibit regular structures, called *regularly interstratified* or *mixed-layer clay minerals*. These minerals are characterized by series or stacks of structural layers in which A-type structural layers (e.g. *mica*/*illite*) occur interspersed with B-type structural layers (e.g. *smectite*).

The basal spacing of the resulting regular interlayer is expressed by $d_{AB} = d_A + d_B$. The regular interlayers of clay minerals from the crystallochemical point of view correspond to true mineral species. Regular interstratifications, such as chlorite-smectite, chlorite-vermiculite, talc-chlorite and biotite-vermiculite, are mentioned in the literature.

Table 6.2 shows the classification and representative species of regular interstratified clay minerals.

Table 6.2 Classification of clay minerals with regularly interstratified structures: interstratifications of alternating layers in 50/50 proportions (*In:* Guggenheim et al. 2006)

1:1	None	Octahedral layer	Mineral species
2:1	Pyrophyllite-smectite	Dioc-dioc	Brinrobertsite
	Talc-smectite	Trioc-trioc	Aliettite
	Talc-chlorite	Trioc-trioc	Kulkeite
	Mica-smectite	Dioc-dioc	Rectorite
	Biotite-vermiculite	Trioc-trioc	Hydrobiotite
	Chlorite-smectite	Trioc-trioc	Corrensite (low charge)
	Chlorite-smectite	Trioc-trioc	Corrensite (high charge)
	Chlorite-vermiculite	Dioc (on average)	Tosudite
1:1 and 2:1	Serpentine-chlorite	Trioc-trioc	Dozyite

Unlike the *regularly interstratified structures*, the *irregularly interstratified structures*, which are much more frequent, are not qualified with names, because they do not have crystalline periodicity, reason why they are not considered true mineral species. Regular and irregular mixed layers I-Sm (illite-smectite) and Sm-I (smectite-illite), i.e. mixed layers between expandable and non-expandable clay mineral species, have been the most studied, the transitions of both structures being used as geological markers in reconstructing the thermal and tectonic history of sedimentary basins.

XRD, TEM and HRTEM are the analytical techniques employed to find out the proportion and sequence of the mixed layering.

K-Sm (kaolinite-smectite) is another interesting mixed layer that has attracted the attention of many researchers.

AIPEA (Association Internationale Pour L'Étude des Argiles) had issued one interesting publication within the AIPEA Educational Series, Fiore S, Quadros J and Huertas FJ being the editors, with a 1st edition issued in 2009 and a 2nd edition issued in 2013. This publication entitled *Interstratified Clay Minerals: Origin, Characterization and Geochemical Significance* provides an overview of this type of clays and gathers contributions of the following researchers: Plançon (2013), Meunier (2013), Nieto and Arroyo (2013), Komadel and Madejová (2013a, b), Ferrell et al. (2013) and Srodon (2013).

6.3.4.2 Clay Minerals of Non-planar Structures

Table 6.4 shows the systematics of the clay minerals of non-planar structures, which are organized into two groups: (1) clay minerals with modulated structures (fibrous sepiolite and palygorskite) and (2) clay minerals with rolled, tubular and spheroidal structures and particle shape (rolled or tubular halloysite, antigorite, chrysotile and allophane-imogolite).

6.3.4.2a: Sepiolite-Palygorskite Group of Clay Minerals

Figure 6.12 shows the crystallochemical features that justify the fibrous crystal habit or shape of the clay mineral *sepiolite*, and Figure 6.13 shows the fibrous

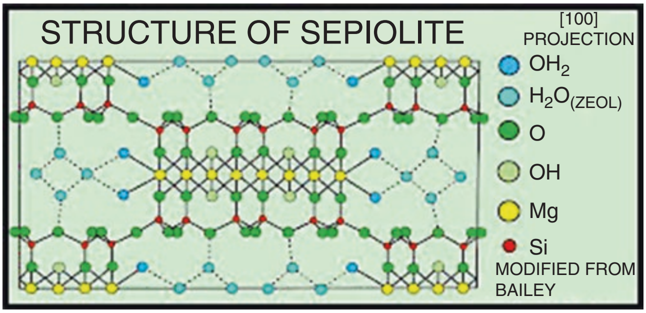


Fig. 6.12 Schematic representation of *sepiolite*'s structure (modified from Bailey 1980a, b)

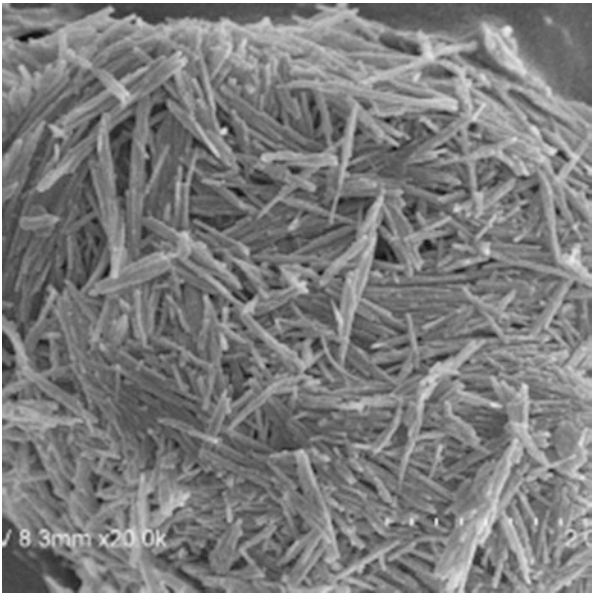


Fig. 6.13 Fibrous morphology of *sepiolite*

particle shape of *sepiolite*. The first attempts to establish the sepiolite structure were carried out by Nagy and Bradley (1955), Brauner and Preissinger (1956), Brindley (1959) and Rautureau and Tchoubar (1976).

Figure 6.14 shows the crystallochemical features of *palygorskite*, and Figure 6.15 exhibits one specimen of *palygorskite* from an occurrence in the Kuzuu district, Japan. Despite the acicular crystal habit, *sepiolite* and *palygorskite* are phyllosilicates inasmuch as they exhibit continuous two-dimensional tetrahedral sheets. However, they just differ from other layer silicates in that they lack continuous octahedral sheets.

The crystal structures of *sepiolite-palygorskite* clay minerals show characteristics of both layer and chain silicates.

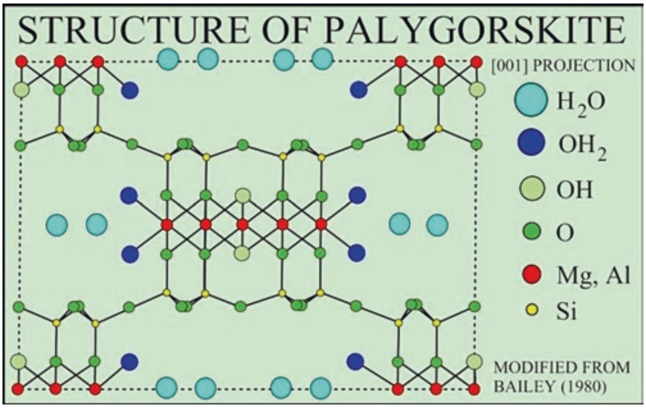


Fig. 6.14 Schematic representation of *palygorskite's structure*

Fig. 6.15 Fibrous morphology exhibited by a palygorskite specimen from an occurrence in the Kuzuu district, Japan

Tetrahedral sheets involve sixfold rings of tetrahedra and present a continuous basal oxygen atom plane; but unlike ideal phyllosilicates, these minerals show apical oxygen atoms pointing along opposing directions (Brigatti et al. 2006).

The essential features of the palygorskite-sepiolite mineral group are apparently:

1. The continuous tetrahedral basal oxygen planes.
2. The inverted tetrahedral arrangement that forms ribbons of joined pyroxene-like chains generate channels visible using HRTEM (Rautureau et al. 1972; Rautureau 1974).
3. The discontinuous octahedral sheet (Guggenheim et al. 2006; Guggenheim and Krekeler 2011).

The name *palygorskite* was attributed by Savchenkov in 1862 and derived from the local name Palygorsk in Ural Mountains, Russia. In industrial and commercial nomenclature, the clay rich in this fibrous clay mineral is called *attapulgite*, a name that was attributed in 1935 by De Lapparent to a clay mineral he encountered in a fuller's earth occurrence in Attapulgus, Georgia, USA.

The name *sepiolite* was used for the first time by Ernst Friedrich Glocker in 1847 and derived from the Greek *sepion* due to its resemblance to the bone of the sepia or cuttlefish characterized by very low weight, whiteness and porosity. The white, soft and light *sepiolite* was originally named "meerschaum" by Abraham Gottlob Werner in 1788 and was initially used to make tobacco pipes known as "meerschaum pipes". The German name "meerschaum" is equivalent to the English name "sea foam" and to the French name "écume de mer".

S*epiolite* particles exhibit fibre shapes (Fig. 6.13). *Palygorskite particles or crystals* also exhibit fibre shape, needle-like, as a rule much thinner than sepiolite particles.

The internal arrangement of the tetrahedral and octahedral sheets in *palygorskite* as well as in *sepiolite* is unique within clay minerals in that there are channels or tunnels through the structure, channels that are filled with zeolitic water. When this water is driven off by heating the surface area and thus the sorptivity is increased, chemical compounds that are of the size that will fit into these channels could be absorbed (Fig. 6.14).

In *sepiolite*, the channels have the dimensions 3.7 × 10.6 Å, whereas in palygorskite, they measure 3.7 × 6.4 Å.

The first attempts to establish the structure of palygorskite were carried out by Bradley (1940), Preissinger (1963) and Drits and Alexandrova (1966).

Sokolova and Drits (1971) have proposed the following chemical composition for *palygorskite*: $(Mg_2,Al_2)Si_8O_{20}(OH)_2(OH_2)_4 4H_2O$. The thermogravimetric (TG) curves show three weight losses attributed to water. The water $4H_2O$ adsorbed on fibres external surfaces or occupying the channels existing in the structure (*zeolitic water*) is removed for temperatures below 200 °C without producing structural changes; the water $(OH_2)_4$ is weakly bonded in the structure (*crystallization water*) and its loss around 300 °C produces significant structural changes; finally the water $(OH)_2$, the *structural water*, being strongly bonded to the octahedral Mg cations is only removed for temperatures higher than 400 °C and produces irreversible structural changes.

As a rule, in *palygorskite*, some Mg is replaced by Fe. Also, some Si may be replaced by Al or Fe. Velde (1992) has proposed for *palygorskite* the following general chemical formula: $(R^{2+},R^{3+})_5(Si,R^{3+})_8O_{20}(OH)_2(OH_2)_4(H_2O)_4$, where R^{2+} may be Mg^{2+} or Fe^{2+}. According to Galán and Carretero (1999), *palygorskite* is intermediate between di- and trioctahedral.

Sepiolite is a related phyllosilicate being also a natural hydrated magnesium phyllosilicate that displays a crystal structure consisting of talc-like ribbons with $Mg_8Si_{12}O_{30}(OH)_4(OH_2)_4(H_2O)_8$ as the ideal chemical formula. It has negligible isomorphous substitutions of Al and Fe for Si. According to Galán and Carretero (1999) and Caillère et al. (1982, 1989), *sepiolite* is a true trioctahedral clay mineral with eight octahedral positions filled with Mg^{2+}.

Garcia-Romero and Suárez (2010) have provided complementary data on the chemical composition of both *sepiolite* and *palygorskite*, *sepiolite* occupying the most magnesic and trioctahedral extreme of the series and *palygorskite* occupying the most aluminic-magnesic and dioctahedral extreme.

In short, the main properties that *sepiolite* and *palygorskite*, the so-called fibrous clay minerals, have in common are as follows: fibre particle shape; fibre sizes vary in length from about 1 to 10 μm; high specific surface area 150–320 $m^2.g^{-1}$;

moderate base-exchange capacity 30–50 meq/100 g; melting point 1550 °C; high sorptivity; high water absorption up to 100% of the clay weight; and oil absorption up to 80% of the clay weight.

With regard to *sepiolite* and *palygorskite* applications quite a lot are known, some are herein being exemplified: pet or cat litter as absorbent; industrial floor absorbents; drilling fluids and paints as a dispersing, anti-settling, thickening and thixotropic additive; pesticides, insecticides and herbicides carriers; animal feed binders; catalyst carriers; cosmetics; pharmaceuticals; foundry sand binders; anti-caking agents. The microporous structure of these clay minerals is important for their applications in nanotechnology (Tang et al. 2012).

Pozo and Galán (2013) had edited an interesting publication that gathers interesting papers on the characterization, origin and applications of magnesium clays. *Sepiolite* in the form of "meerschaum" is utilized for pieces of jewellery and pipe bowls.

Ruiz-Hitzky et al. (2013a, b) within other applications emphasize the interest of *sepiolite* and *palygorskite* for bioplastics and membranes, uses in biomedicine as drug delivery systems and adjuvants of vaccines as well as in tissue engineering.

Very recent studies carried out by Ruiz-Hitzky et al. (2017) show how *sepiolite* and *palygorskite* fibrous clay minerals can be incorporated, as efficient fillers, into polymer matrices, not only to improve their mechanical properties, but also to provide functionality to the resulting polymer-clay nanocomposites.

The use of pharmaceutical-grade clay minerals as carriers of pharmaceuticals has particular advantages due to their biocompatibility, low toxicity and precise tailorability of surface properties. Also, clay minerals' rheological properties allow them to act as emulsifiers and stabilizers of pharmaceutical formulations and also as suspending agents for hydrophobic drugs.

Another important effect of some clay minerals is the retarded release of surface adsorbed pharmaceuticals, helping to modulate the drug release profile (Aguzzi et al. 2007). Controlled drug delivery is required to avoid overdosing or underdosing episodes during the therapeutic use.

The peculiar morphology and textural characteristics of *sepiolite* and *palygorskite* make these silicates appropriate as fillers in polymer matrices providing the reinforcement of these materials and improving their structural properties.

In the pharmaceutical industry, *sepiolite* is known as magnesium trisilicate and by the trade names Alenic Alka® and Recip®. In the pharmaceutical industry, *palygorskite* is known as *activate attapulgite* and magnesium and aluminium silicate and by the trade names Attaclay®, Attagel® and Attapulgite®.

Palygorskite and *sepiolite* are usually formed in shallow low-energy depositional environments such as estuaries and marine lagoons.

The largest commercial *sepiolite* deposit in the world is at Vicalvaro, Vallecas, near Madrid, in Spain, a country that is the largest producer of *sepiolite* clays in the world. In Vicalvaro's deposit, *sepiolite* occurs in layers with thickness ranging from 1 m to 5 m. In the world, most of sepiolite and *palygorskite* deposits are dated of Early Eocene. In Portugal, *palygorskite* characterized by long fibres occurs in some sites of the Lisbon Volcanic Complex.

Attapulgite is a commercial and industrial name that was attributed for the first time by De Lapparent in 1935 to the *fibrous clay* that occurs in Attapulgus, Georgia, USA. Also, in Portugal, very small occurrences of *sepiolite* are known. The variety of *sepiolite* called *xylotile* characterized by the partial substitution of Mg by Fe was identified in a gabbro quarry in Ribamar, Ericeira (Gomes 1992).

AIPEA (Association Internationale Pour L'Étude des Argiles) had issued in 2013 one interesting publication within the AIPEA Educational Series, Pozo M and Galán E being the editors. This publication entitled "Magnesium Clays: Characterization, Origin and Applications" provides an overview of this type of clays and includes contributions of the following authors: Guggenheim (2013), Calvo and Pozo (2013), Pozo and Galán (2013), Pozo and Calvo (2013), Tosca (2013) and Santarén (2013).

6.3.4.2b: Allophane-Imogolite: Group of Quasi-Amorphous Clay Minerals

Allophane-imogolite is the name of a group of clay-size poorly crystalline hydrous aluminosilicates characterized by short-range structural order, which are commonly found in soils formed from volcanic ash and weathered pumice. However, cases are known of *allophane* occurrences not associated to soils, for example, in precipitates from highly acidic silica-rich springs.

Occurrence, nature and properties of *allophane* and *imogolite* can be found in reviews such as those published by Parfitt (1990) and Harsh (2000). The association of *allophane* and *imogolite* with soils of volcanic origin arises from the fact that ash, tephra and other pyroclastic materials contain amorphous materials that can rapidly release Al and Si.

In *allophane*, the Al/Si ratio varies in the range of 1–2. *Allophane* and *imogolite* provide broad and diffuse diffraction maxima in their XRD patterns.

Allophane exhibits when observed in HRTEM (High Resolution Transmission Electron Microscopy) nanometric hollow spherules, whereas *imogolite* exhibits hollow tubules forming bundles of several micrometres in length. The internal diameters of *imogolite* nanotubes are around ~1 nm, significantly smaller than *halloysite* nanotubes' internal diameters (20–100 nm), but enough high to host most of the drug molecules.

In a recent scientific article entitled "Health and Medical Applications of Tubular Clay Minerals", Aguzzi et al. (2016) present an up-to-date and very interesting review of the effective and possible applications of *halloysite* and *imogolite* in nanopharmaceutics.

6.3.4.3 Systematics of Clay Minerals

Tables 6.3 and 6.4 show the systematics internationally adopted and established in 1966 by AIPEA ("Association Internationale pour L'Étude des Argiles") and in 1963 and by CMS ("Clay Minerals Society") for *clay minerals* exhibiting planar and non-planar structures, respectively:

1. The organizational model (layer type) of the fundamental structural unit (*unit cell*), and within layer type, by groups based on *electric charge p.f.u* (*electric

charge per formula unit) expressed by the letter *x* and as a positive number, representing the net negative charge per unit layer.
2. The groups are divided by subgroups based on the occupation, *dioctahedral* or *trioctahedral*, of the structural octahedral sheet.
3. Each group and subgroup being represented by species based mainly on chemical composition.

The net negative layer charge is balanced by the positively charged interlayer material.

6.4 General Notes on Clay Typologies and Main Properties

Clays and *clay minerals* most probably started being formed on Earth immediately after planetesimal formation (Hazen et al. 2013). Indeed, the necessary conditions for clay minerals formation, the existence of water, sources of acids and aluminosilicate rocks, would have prevailed on the early Hadean Earth.

There are several clay types based on geological, technological and commercial arguments, such as primary or residual clay, and secondary or sedimentary clay; expansive clay; plastic clay; absorbent clay; refractory clay; nanoclay; special clay (ball clay, bentonite, kaolin, fuller's earth, fibrous clay, fire clay and flint clay); and common clay (pottery clay and heavy clay):

1. Primary or residual clay
2. Secondary or sedimentary clay
3. Special clay: ball clay, bentonite, kaolin, fuller's earth, fibrous clay (sepiolite and palygorskite), and "flint" or "hard" clay, and refractory clay
4. Common clay: pottery clay, structural construction clay and heavy clay (the last two clay types being used for the manufacture of brick and of roof and floor tiles)

The nomenclature referred to encompasses geological and commercial names and typologies attributed to natural clays used as they occur or after being submitted to some kind of simple industrial processing comprising refining (involving physical processes) plus beneficiation (involving chemical processes).

The largest and highest-quality primary or *residual kaolin* deposits in the world are located in Cornwall and Devon in south-western England, *kaolinite* being derived from late-stage magmatic or hydrothermal alteration or decomposition of feldspar in the granite, and the *kaolinite* content in the altered granite ranges between 10 and 20%. The largest and highest-quality secondary or sedimentary *kaolin* deposits occur in the Amazon region in northern Brazil and in Georgia, USA. The clayey products of the weathering of source or mother crystalline rock were transported by several streams.

The main natural deposits of *kaolin* composed by *tubular halloysite* are from Dragon Mine and Matauri Bay in Utah (USA) and Northland (New Zealand), respectively. Tubular halloysites are being used for the development of innovative nanomaterials useful for biotechnological applications, such as controlled release of drugs (Shutava et al. 2014; Wei et al. 2014; Lvov et al. 2016; Cavallaro et al. 2015), tissue engineering (Fakhrullin and Lvov 2016), oil recovery and eco-compatible packages.

The name *kaolin* is derived from Kauling or Gaoling, in Jiangxi province of China, where Chinese geologists discover that the local kaolin deposit is derived from the alteration of a granite stock of Middle Jurassic age (Chen et al. 1997).

Kaolin is a basic raw material for the manufacture of traditional white ceramics (porcelain stoneware, earthenware), paper filler and coating and of many modern materials such as nanocomposites, although the most well-known product, the sophisticated porcelain from Jingdezhen, Jiangxi, China, is manufactured from 2000 years ago up to the actuality. Gaoling Shan, translated literally as "high ridge", is located at about 40 km to northeast of the city of Jingdezhen, and there was the first mining site of *kaolin* clay.

Special clays relative to *common clays* are characterized, as a rule, by the following specificities:

1. Less number and smaller dimension of clay deposits.
2. Simple composition although requiring more complex and expensive processing.
3. Higher commercial unit value of the respective manufactured products.

With regard to the so-called industrial clays, Harvey and Lagaly (2013) have proposed four categories:

Category 1: High-quality, high-technology clays requiring major investment for large tonnage production to supply both local and international markets.

Examples of industrial clays classified into category 1: the sedimentary kaolin deposits with large occurrences in the south coast of Georgia, USA; the hydrothermal kaolin deposits of Cornwall, UK; and the sedimentary kaolin deposits of the Amazon basin, Brazil.

Category 2: Unique specialty clays requiring advanced mining and processing technologies for small tonnage niche markets, locally and internationally.

Examples of industrial clays classified into category 2: the low-temperature hydrothermal alteration of volcanic ash halloysite deposits of Northland, New Zealand; the hectorite Li- and Mg-rich smectite deposits (bentonite) with occurrences in the USA, derived from hydrothermal alteration of basaltic ash; and the white bentonite deposits occurring in some countries.

Category 3: Relatively low-technology clay of moderate quality that mainly supplies local markets.

Examples of industrial clays classified into category 3 are worldwide frequent, characterized by not rigid specifications and moderate-grade processing; all known deposits of category 1 clays contain associated category 3 clays, as are the cases of kaolins from Georgia, USA, and Cornwall, UK; kaolin deposits from the Czech Republic, Ukraine, Germany, France and Spain, as well as the filler-grade kaolins of Indonesia, and the bentonite deposits of Wyoming, USA, could be classified into category 3.

Category 4: Comprises industrial clays of variable but low quality, the applications requiring low-technology; the low-quality materials may justify little or no processing, nevertheless suitable for large-tonnage local markets; some clays of category 4 may be of moderate to high quality but for one or more reasons considered non-economic; these reasons may include isolation from markets, politically or economically unstable locations and unfavourable legislative environment.

Examples of industrial clays included in category 4 are the numerous small-size deposits of kaolin, bentonite, ball clay, fibrous clay and heavy clay with occurrences in most countries of the world, mined and particularly used in ceramics.

It matters to say that on the industrial applications of clays, Robertson (1960) was a real pioneer.

Kaolin is a naturally occurring clay-rich material that geologically corresponds to a rock dominated by *kaolin group minerals*, a group that comprises four mineral species: *kaolinite*, *halloysite*, *dickite* and *nacrite*, expressed by a basic T:O or 1:1 layered structure and the chemical formula $Al_2Si_2O_5(OH)_4$.

In terms of volume of geological deposits and applications importance, *kaolinite* and *halloysite* are really important species of the *kaolin group minerals*. *Kaolinite* and *halloysite* are secondary minerals frequently formed by the action of weathering processes upon aluminous felsic igneous and metamorphic rocks. *Dickite* and *nacrite* geological occurrences are extremely small and rare, being related to hydrothermal alteration processes of primary rock-forming minerals, such as potassium feldspars and micas.

The geological, geomorphological and geochemical environment favourable to primary or residual kaolinization (origin meteoric, hydrothermal, hydrothermal/meteoric) should satisfy the following criteria referred to by Gomes (2002):

1. Removal of Ca^{2+}, Mg^{2+}, Na^+ and K^+ from the precursor mineral silicates, particularly tectosilicates exemplified by feldspars (mainly microcline and orthoclase) and phyllosilicates exemplified by micas (muscovite and biotite), which requires (a) precipitation exceeding evaporation; (b) drainage systems facilitating the leaching and removal of alkaline and calc-alkaline cations; (c) mother rock (mainly granite, granodiorite and gneiss) showing fracturation and fissuration; (d) water easy percolation; (e) oxidation of Fe^{2+} to Fe^{3+}; and (f) climate alternation, dry season alternating with moist season
2. Acidic environment, which requires (a) aqueous fluids, as is the case of meteoric water, containing CO_2 in solution and with origin in the air and organic acids derived from organic matter decomposition and (b) hydrothermal liquids and gaseous fluids containing SO_2, N_2, HF, CH_4, NaCl, KCl, etc.
3. High Al/Si ratio, which requires (a) Si mobilization and removal in acidic environment and (b) Al immobilization and concentration in acidic environment and formation of Al-OH or Al-Si-OH polymers

Bentonite is a rock term defined by Ross and Shannon (1926) as a clay material resulting from the alteration of glassy igneous rocks, usually volcanic ash. According to Christidis and Huff (2009), bentonite deposits could be formed by the following three mechanisms:

1. Diagenetic alteration of volcanic glass in an aqueous environment.
2. Hydrothermal alteration of volcanic glass.
3. Formation of smectite-rich sediments in salt lakes and in salt-rich environments.

The geological, geomorphological and geochemical environment favourable to primary or residual smectization or montmorillonization (origin meteoric, hydrothermal, hydrothermal/meteoric) should satisfy the following criteria referred to by Gomes (2002):

1. Retention of Mg^{2+}, Ca^{2+}, Fe^{2+} and Na^{+} derived from precursor minerals dissolution, which requires (a) evaporation exceeding precipitation, (b) mother rock showing little or moderate permeability, (c) prevailing alkaline environment and (d) no or little oxidation of Fe^{2+} to Fe^{3+}.
2. Precursor minerals characterized by high specific surface area and high susceptibility to hydrolysis, which requires (a) easily alterable glassy rocks, such as ash and volcanic tuff.
3. Low Al/Si ratio, which requires (a) Al less mobile than Si and (b) Si fixation under the form of cryptocrystalline silica (cristobalite).

Bentonite is mainly composed of clay minerals of the *smectite group* minerals, *montmorillonite* being the most frequent species.

Grim and Guven (1978) had used the term *bentonite* for any clay which was dominantly composed of clay minerals of the smectite group without regard to its origin. Bentonite is named after Fort Benton, Wyoming, USA, where its largest sources are found. The name of its principal clay mineral, *montmorillonite*, comes from Montmorillon, France, where it was first found. Greece, the USA and Turkey are the countries' major producers of *bentonite*.

Bentonite has a variety of properties provided by its major clay mineral: high adsorption and absorption capacities, high pore volume, high specific surface area, high intra-crystalline swelling capacity and high water retention capacity. The thixotropic behaviour is an important property of bentonite; when products containing bentonite as additives are shaken and stirred, they can change from gelatinous to liquid state; and at rest again gel is formed.

The originally hydrophilic bentonite surface can be made hydrophobic. This will allow the complete dispersion of silicate platelets in organic solvents.

For the production of organophilic bentonites, quaternary alkyl ammonium compounds are used. The exchange of interlayer cations results in products which are used to modify the rheology (e.g. the thixotropy) of organic solvents, oils, fats, ointments and plastics.

Bentonite is widely used as an essential thickener and extender for paints. Also, it is used in drilling muds; the drilling fluid acts as a lubricant to reduce the friction between the drilling string and the hole walls. Also, the circulation of the drilling fluid can cool the bit, can bring the drill cuttings from beneath the bit up to the ground surface and can produce an impermeable filter cake on the hole walls.

In civil engineering construction, bentonite dispersions by injection can be used to grout cracks and fissures in rocks and can be added to waterproof concrete walls and floors or added to mortar to increase its plasticity (Harvey and Lagaly 2013).

Bentonite natural properties can be changed (for instance, the rheological properties) by a process called activation. It is the case of alkali or soda activation that uses sodium carbonate (Na_2CO_3) to transform the calcium/magnesium bentonite into the sodium form. To achieve such modification, bentonite with water contents of 35–40% (m/m) is usually kneaded or milled with 1–5% (m/m) sodium carbonate and homogenized.

Many bentonite applications require hydrophobization which is currently achieved using the reaction of bentonite with quaternary ammonium salts such as dialkyl dimethylammonium, dialkyl benzyl-methylammonium and alkyl benzyldimethylammonium salts.

Bentonite can be used in environmental applications, such as filtering, decolourizing, clarifying, and pelletizing animal feed, and can be used too as pet litter adsorbent and pesticide carrier. Bentonite also plays an important role in the development of health products, such as cosmetics and pharmaceuticals (Viseras et al. 2010).

Fuller's earth is a sedimentary clay assumed as being the alteration product of volcanic ash deposits in seawater that shows characteristics close to those of bentonite, Ca-montmorillonite being its main constituent clay mineral; its name is derived from its earlier use as fulling or cleaning of the grease from wool clothes; the name *fuller* derives from the Latin name fullon attributed to the person whose job was the degreasing of dirt clothes. Within the Romans the *fullon* used to first steep into urine (alkaline liquid rich in ammonia) the pieces of cloth, some time after the pieces were placed into a basin containing a slurry of *fuller's earth* (*creta fullonia* in Latin), and finally they were washed with fresh water (Robertson 1986).

Fuller's earth is a low plastic clay characterized by its bleaching capacity used to filter animal, mineral and vegetable oils. It is used too as a bonding agent for foundry sands and in the manufacture of carbonless copy paper.

In the UK, *fuller's earth* deposits occur in the Redhill-Nutfield area in Surrey and in Bedfordshire. In the USA, there are extensive deposits in Georgia.

Fuller's earth is used to treat dye solutions used for colouring clothes from the textile industries (Khan et al. 2018).

Bleaching earth is a type of modified clay behaving similarly to *natural fuller's earth* that is used in certain industrial applications. It is usually produced from the treatment of Ca-bentonite with hydrochloric acid or with sulphuric acid, the calcium ions being replaced by hydrogen ions. Acid-activated bentonite comparatively to non-activated bentonite is characterized by an increase of specific surface area, porosity and surface acidity. It has been a traditional product for several decades used in bleaching or decolourizing applications, for instance, as adsorbents for oil and wine clarification, and as catalysts too particularly in the case of pillared smectites (Kendall 1996; Bovey et al. 1996; Falaras et al. 1999; Pagano et al. 2001; Komadel 2003; Onal and Sarikaya 2007).

Ball clay, a term of English origin in the eighteenth century, by definition is a kaolinitic sedimentary clay that commonly consists of 20–80% kaolinite, 10–25% mica/illite and 6–65% quartz. As a rule, kaolinite is structurally disordered, reason why it is called kaolinite D.

Ball clay, as a rule, occurs as clay seams, and in the same deposit, variations in clay composition also occur, including the quantity of the major minerals, accessory minerals and carbonaceous materials such as lignite. *Ball clay* is formed from the weathering of granite and granitoid rocks, the weathering products being washed and transported by ancient rivers and streams from upland grounds to sedimentary basins located in nearby low-lying grounds where they settle down and form various overlaying clay seams showing both vertical and lateral variation in composition and granularity.

Ball clay is an extremely rare mineral resource found in very few places around the world. Its name dates back to the early methods of mining when specialized hand tools were used to extract the clay in rough cube shapes of about 30 cm. As the corners were knocked through handling and storage, these cubes became rounded and "ball" shaped. *Ball clay*, a fundamental raw material of great importance in white ceramics (fine tableware porcelain, electric porcelain, stoneware, earthenware, sanitary ware, floor tiles and wall tiles of white or nearly white ceramic bodies), is sometimes referred to as highly plastic clay of grey, light brown or black colour that changes to almost white colour after firing. High plasticity, high refractoriness, excellent workability, controlled organic content and controlled rheology are *characteristic* properties of ball clay.

Ball clay content in the ceramic formulations, e.g. in fine porcelain, as a rule is 2–4%, whereas in sanitary ware and in earthenware the contents could attain 40%. Mitchell and Vincent classified worldwide ball clay deposits, mainly formed during Lower Tertiary, into four categories, based on reserves and quality (Worrall 1982; Gomes 2002).

Internationally, deposits of ball clay of high quality are much rarer than those of kaolin. The principal traditional ball clay deposits occur in the southwest of England, in the Bovey and Petrockstow basins in Devon and in the Purbeck and Wareham in Dorset. There are also important deposits of *ball clay* in Westerwald in Germany; in Skalna and Cheb in the Czech Republic; in the Mississippi basin with occurrences both in Western Tennessee and in Jackson/Purchase, Kentucky, USA; and in the Charentes and Provins basins in France.

Fire clay, a term of English origin and related to the clay high refractoriness and to its geological occurrence, is defined as sedimentary clay of refractoriness not lower than 1,500 °C, and that after firing shows light brown, light grey and ivory colours. The traditional fire clay from the Yorkshire in England occurs immediately under the "coal seams" or "coal measures" dated of the Carboniferous, reason why the fire clay is also called *underclay*. *Fire clay* is essentially composed of disordered kaolinite or kaolinite D, mica/illite, quartz, illite-montmorillonite mixed layers and organic matter, sometimes with dickite associated (Gomes 2002; Worrall 1975, 1982). *Fire clays* are utilized to manufacture tableware, stoneware and ornamental ceramics.

Refractory clay is a type of clay still more refractory than the fire clay, however distinct in matter of geological occurrence. Refractory clays comprise the so-called flint clay or hard clay, and the *semi-flint clay* or *semi-hard clay*. These clays are kaolinite-rich, the kaolinite content could reach values higher than 95%, and sometimes show associate free aluminium hydroxides, *gibbsite* and *boehmite*, and iron oxides/hydroxides, *goethite* and *hematite*.

Interesting examples of flint and semi-flint clays are the deposits of karst bauxite reported by Gomes (1966a, b, 1968), Valeton (1983), Bardossy (1982), Combes and Bardossy (1995) and Putzoulu et al. (2018).

Synthetic clay minerals with well-designed chemical composition, structure and morphology under controllable synthetic conditions possess much improved properties in comparison with their natural counterparts and have practical applications. *Synthetic clay minerals* provide new choices of layered solids and can be tailored to promote specific properties. They provide better understanding of the various processes involved in the formation of natural mineral counterparts.

Carrado et al. (2006) and Zhang et al. (2010) summarize and discuss the recent advances on synthetic clay minerals such as *kaolinite*, *pyrophyllite*, *mica*, *smectite*, *chlorite* and *sepiolite*. The first group of authors present and discuss the variables of clay minerals synthesis, with an emphasis on starting materials and hydrothermal conditions.

The first attempts to synthesize clay minerals go back to the 1950s of the twentieth century, well represented by the works of Caillère et al. (1953, 1954, 1955). In fact, kaolinite and several species of smectite have been synthesized during the last 70 years from diverse starting materials, mostly other aluminosilicates, glasses and gels. Regarding *smectites* synthesis, Kloprogge et al. (1999) summarize, evaluate and criticize the various approaches to smectites synthesis being adopted and the long-term stability of the obtained products. Clay minerals synthesis is generally performed either at low temperature or at a higher temperature by hydrothermal technology. New high-tech products derived from these synthetic clay minerals are being developed in China.

Examples of *synthetic clay minerals* commercially produced in China are referred to by Zhou et al. (2016): *synthetic hectorite* (the ideal chemical composition $Na_{0.50–1.20}[(Mg_{5.50–4.80}Li_{0.50–1.20})(Si_{8.00})O_{20}(OH)_4]$) (Zhou et al. 2005; Zhang et al. 2010), *synthetic saponite* ($Na_{0.50–1.20}[(Mg_{6.00})(Si_{7.50–6.80}Al_{0.50–1.20})O_{20}(OH)_4]$) (Zhang et al. 2010) and *synthetic mica* (Chen and Peng 1990).

It is worth pointing out that *synthetic hectorite* comparatively to natural *montmorillonite* offers the general benefits of higher rheological efficacy (viscosity and yield value), lower iron content and lighter colour.

Hectorite clay and *hectorite organoclay* have less antiperspirant potential than montmorillonite-based products. The *hectorite* particle platelets are much smaller and elongated compared to the more equidimensional montmorillonite platelets. Therefore, *hectorite clay* has more platelets per gram providing greater swelling capacity and improved rheological efficiency compared to *montmorillonite clay*.

Hydrotalcite, also called *anionic clay*, is not a real clay mineral but has a layered structure and properties similar to those that characterize clay minerals. Hydrotalcite

Fig. 6.16 Schematic structure of *hydrotalcite*. The symbol $_x$ indicates the possibility of isomorphous substitution of Mg for Fe^{2+}, Zn^{2+}, Cu^{2+}…, and Al for Fe^{3+}, Cr^{3+}…

$$Mg_{1-x} \ldots\ldots Al_x \ldots\ldots (OH)_2$$

$$\ldots\ldots H_2O \ldots\ldots CO_3 \ldots\ldots H_2O$$

$$Mg_{1-x} \ldots\ldots Al_x \ldots\ldots (OH)_2$$

is a layered double hydroxide (LDH) whose name is derived from its resemblance with the clay mineral talc and is characterized by its anion-exchange properties and high water content. *Hydrotalcite* is a magnesium-aluminium hydroxycarbonate with the formula $Mg_6Al_2(OH)_{16}CO_3.4H_2O$ and constituted of positively charged brucite-like $Mg(OH)_2$ layers intercalating mobile anions, as a rule CO_3^{2-} (Fig. 6.16). The natural form of *hydrotalcite* was identified in a serpentine-magnesite deposit associated to serpentine, dolomite and hematite in the Snarum area of Norway and exhibits white or pearl-like colours. The synthetic form of *hydrotalcite*, a high-temperature chemical sorbent, started being produced since 1966, and is used in pharmacy as antacid, and in industry as sorbent, as sunscreen for UV absorber, as catalyst support, and as intercalator of polymeric chains, and in environment protection.

Various scientific articles show the main properties and applications of hydrotalcite and of the class of lamellar inorganic solids with structure similar to hydrotalcite structure, called "layered double hydroxides (LDHs)": Leroux and Besse (2001), Wang and O'Hare (2012), Mishra et al. (2018) and Revuri and Lee (2019).

6.5 General Applications of Clay and Clay Minerals

Clays and clay minerals most probably started being formed on Earth immediately after planetesimal formation (Hazen *et al*. 2013). Indeed, the necessary conditions for clay minerals formation, the existence of water, sources of acids and alumino-silicate rocks, would have prevailed on the early Hadean Earth.

Both main fields of interest and applications of clays are schematically shown in Fig. 6.17.

Clay and naturally stone have been used by humans since the Stone Age due primarily to the fact that clay and stone are quite common at the Earth's surface and are utilized for agriculture (clay is a fundamental component of soil), ceramics and building materials.

Ceramics is the main and conventional field of clay application worldwide. Any clay could be used in ceramics. Dondi et al. (2014) propose a simple technological classification of clay raw materials used in ceramics based on chemical (Fe_2O_3 content) and mineralogical parameters (content of phyllosilicates and carbonates) together with particle size (fractions <2 μm and >63 μm) and plasticity (methylene blue index and Atterberg plastic index). The chemical argument could firstly

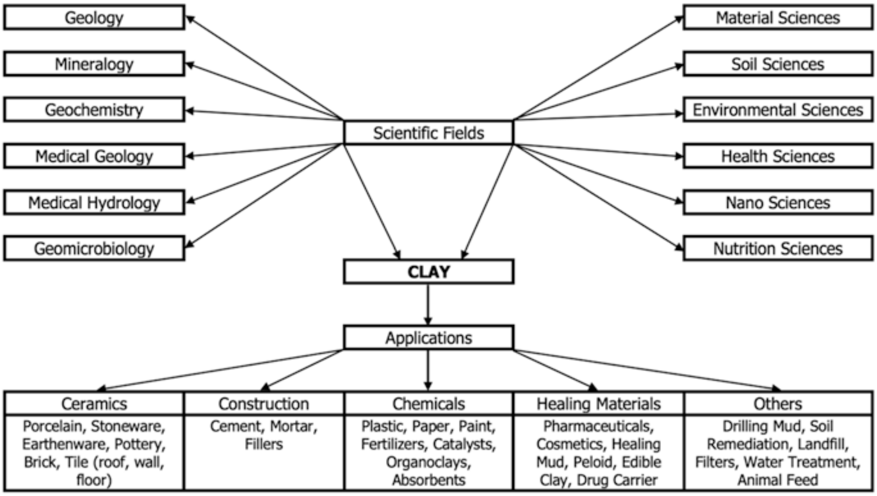


Fig. 6.17 Scientific fields and traditional areas of clay application

discriminate light-firing and dark-firing clays just using a total iron oxide threshold of 3%.

Light-firing clays are distinguished by the amount of kaolinite group minerals and plasticity in “kaolins” (high-grade, low-grade, raw kaolins and kaolinitic clays) and in “plastic clays” (ball clays, pyrophyllitic clays, white bentonites).

Dark-firing clays are classified according to grain size and carbonate contents in carbonate-rich types (marls), red loams and red clays. These clays could be further differentiated by the relative abundance of clay minerals.

Clays are differentiated on the basis of the so-called clay general properties, such as colour; granularity assessed by particle size distribution; specific surface area assessed in $m^2.g^{-1}$ that can change from types to types, from 10 $m^2.g^{-1}$ (in the case of kaolin) up to 300 $m^2.g^{-1}$ (in the case of *fibrous clays*) and even up to 800 $m^2.g^{-1}$ (in the case of total exfoliated or delaminated *smectite clays*); ionic exchange capacity (cation and anion exchange); viscosity; and plasticity. All these clay properties, which are which are commanded by clay minerals crystallochemistry, condition all clay applications.

Within all geological resources, clay is the one that has the most diverse applications, and with the new developments in geology and materials science new insights into the field of clay applications are getting through.

Clay mineralogy and geochemistry and the new developments in analytical methods and procedures can provide useful information for reconstructing and interpreting paleoclimates and even the processes involved in the evolution of extraterrestrial environments (Pearson 2002; Zhou and Keeling 2013).

The interest for clay minerals is particularly due to their biocompatibility and ecocompatibility, low toxicity for oral administration, low cost and natural availability. There is increasing interest and research in the use of clay minerals as agents able to carry specific and functional drugs adsorbed or absorbed to be delivered to target sites in the human body and released in controlled manner. A recent article by Massaro et al. (2018) is a good review of the use of some clay minerals, halloysite in particular among the plethora (about 70 species) of clay minerals, as natural resources for drug carrier applications.

As aforesaid, Fig. 6.17 shows the main and traditional areas of clay interest and application, both scientific and technological. Two scientific areas mainly deal with both positive and negative interactions of *clay* and *clay minerals* on human health. One is *Medical Geology* whose definitions, targets, methods and applications have been referred to and commented in previous topics dealt with in this book. The other is *Medical Hydrology*, a scientific field that studies the impact of mineral water, particularly natural mineral water from thermal spas on human health, and studies too the so-called healing muds and peloids which formation is highly dependent from water, clay being an important constituent of them. Most of the goals, methods and applications of *medical hydrology* will be dealt with in Chaps. 7 and 14 of this book.

Schoonheydt (2016) states that the production of clay minerals for industrial and environmental uses continues to grow annually, and new possible applications for clay minerals are continuously being explored, the author enhancing three areas of application:

1. Clay-polymer nanocomposites, including clay-biopolymer nanocomposites
2. Hybrid clay mineral films with special optical and electrochemical properties
3. Heterogeneous clay mineral catalysts, including bioreactive clay minerals

Schoonheydt (2016) states too that for such purposes the natural clay minerals comparatively to the corresponding synthetic clay minerals suffer from several disadvantages, such as presence of impurities and inhomogeneities in particle size and shape as well as in electric charge distribution.

Clays are important industrial rocks, and as a rule, before their commercialization, they have to undergo industrial processing in order to improve the essential physical and chemical properties required for specific applications, such as:

1. *Purity* (appraised on the basis of mineralogical and chemical data improved by the removal of impurities in order to increase the clay mineral content)
2. *Texture* (particle size and shape); *colour*; *cation and anion exchange*
3. *Hydration and swelling*; *plasticity* (controlled by the clay mineral nature, the amount of water, the particle size distribution and particle shape)
4. *Rheology* (viscosity and thixotropy)
5. *Organic reactions* (via ion exchange, via replacement of interlayer water molecules by polar organic molecules, and via grafting reactions too)

Clay processing may involve various physical or chemical treatments such as wet grinding and gritting, magnetic separation, selective flocculation, froth flotation and activation with inorganic or organic compounds.

Christidis (2011, 2013) reports the relevant properties and the laboratorial or industrial procedures currently used to assess industrial clays and to improve clay quality and grade. Some other reports on clay properties and applications have been provided by the following authors: Robertson (1960), Grim and Guven (1978), Jepson (1984), Odom (1984), Scott (1990), Galán (1996), Psyrillos et al. (1999), Pruett and Pickering (2006), Laird (2006), Murray (2007), Bergaya and Lagaly (2007), Bergaya et al. (2011), and Bergaya et al. (2013).

For instance, with regard to kaolin as basic raw material for ceramics, paper and many other industrial applications, the following properties are essential: whiteness, brightness, refractoriness, chemical inertness, softness, hydrophobicity, fine particle size, easy dispersion in water, water slurries with low viscosity and high solids content, low abrasiveness, low electrical conductivity and low shrinkage.

Clay minerals can play important roles in the environment protection. They have been used in the disposal and storage of hazardous chemicals as well as in the remediation of polluted water. The use of clay minerals as adsorbents for the adsorption of various hazardous substances from aqueous systems, such as heavy metals, dyes, antibiotics, biocide compounds and other organic chemicals (Dal Bosco et al. 2006; Mukherjee 2013; Bhattacharyya et al. 2014; Ismadji et al. 2015; Uddin 2017). The last author referred to has produced an interesting review about the progress in one decade (2006–2016) of the adsorption of heavy metals by clay minerals and confirmed that both natural and modified forms of clay minerals have excellent feasibility in removing different toxic aquatic metal pollutants.

Concerning the application of clays and clay minerals in pharmacy and in therapeutics, there is much more ancient and recent scientific information.

The benefits of clays to human health are well documented in several recently published articles: Robertson (1986, 1996), Novelli (1996, 1998, 2000), Reinbacher (1999, 2003), Viseras and Lopez-Galindo (1999), Veniale (1996, 1998, 1999), Carrtero (2002), Veniale et al. (2004, 2007), Gomes and Silva (2007), Tateo et al. (2006, 2009), Carretero and Pozo (2007), Viseras et al. (2007), Gomes et al. (2009, 2013a, b), Rautureau et al. (2010), Kikouama and Baldé (2010), Fioravanti et al. (2011), De Vos (2010), López-Galindo et al. (2011), Peiró and Tejero (2014), Williams and Hillier (2014), Gomes (2015) and Awad et al. (2017).

Regarding the books, all of a general character, the authors of some of them are herein mentioned: Selinus et al. (2005), Gomes and Silva (2007), Carretero and Pozo (2007) and Rautureau et al. (2010, 2017).

Within all clay typologies, *kaolin*, *bentonite* and *fibrous clays* (*sepiolite* and *palygorskite*) are the clays most interesting in terms of applications in *geopharmacy* and *geotherapeutics*.

Kaolin and bentonite are special types of clay having unique properties of widespread technological importance and traditional applications such as ceramics (porcelain, earthenware, tableware and sanitary ware), paper coating, plastics, pharmaceuticals, paints and cosmetics.

New kaolin applications include nano-sized materials for use in the inks of modern printers, nontoxic pesticides in organic farming and polymer composites used in the packaging industry; in the future, expectations are great in the field of nanocomposites derived from *kaolins* to improve the rheological, thermal and organic complexation capabilities of products used in engineering and medicine, in the last case to carry and deliver pharmaceuticals by using nanotubes of *halloysite* as a Trojan horse (Schroeder and Erickson 2014).

With regard to kaolin and kaolin minerals, Awad et al. (2017) in an excellent article entitled "Kaolinite in Pharmaceutics and Biomedicine" comprehensively and exhaustively report their applications in health-care uses, especially in the pharmaceutical, cosmetic and biomedicine industries.

In the pharmaceutical industry, *kaolin* and *kaolin minerals* in particular are used as active ingredients or as excipients. In the case of *kaolinite*, both as active ingredient and excipient, the action of this clay mineral is attributed to its adequate physical, chemical and surface physicochemical properties. The most important functionalities of *kaolin* or *kaolinite* as excipients in pharmaceutical formulations are as follows: diluent, binder, disintegrant, pelletizing and granulating, amorphizing, particle film coating, emulsifying and suspending agent. Also, the most important functionalities of *kaolin* and *kaolinite* as active ingredients are due to their safe bioactivity, enabling their use in topical applications as haemostatic agent, as dermatological protector and anti-inflammatory agent, and in oral applications as gastrointestinal protector, antibacterial, antiviral, detoxification and antidiarrhoeal agent.

Kaolinite is the most commonly used geophagic clay mineral, especially in tropical areas (Wilson 2003). In other parts of the world, geophagists consume clay or clayey soil rich in *smectite* and *mixed clay mineral assemblages*.

Awad et al. (2017) report that in pharmacopoeias (USA Pharmacopeia 32, British Pharmacopeia BP 2009 and 2012, and European Pharmacopeia PhEur 6.3 monograph 0503 and 7.0 volume 2), kaolin is described as a native hydrated aluminium silicate, powdered and freed from gritty particles by elutriation. The British Pharmacopeia (BP) 2009 considers three kaolin grades: light, light natural and heavy.

With regard to bentonite, numerous research articles exist disclosing the use in many cultures of this type of clay, both externally and internally, for maintaining body health or treating some diseases. Published in PubMed about 100 articles have been produced on the effects of bentonite on human body function.

Detoxification is one of the bentonite effects on body function. This property is referred to its polycationic nature which leads to absorption of negative charge toxins (Williams et al. 2009).

Bentonite is being used in humans as a dietary supplement to prevent and cure *aflatoxin* toxicity. Aflatoxins are poisonous and cancer-causing chemicals that are produced by certain moulds which primarily affect the liver. Bentonite has been recognized as a reliable treatment for pesticides and metal toxicity or poisoning if the clay mineral *montmorillonite* is supplemented in diet. Bentonite has been used in the treatment of diarrhoea and other affections of the gastrointestinal tract that, for instance, can produce borborygmi – the stomach rumblings caused by gas moving through the intestines, the driving force of the treatment with bentonite being the attractive power of clay-particle surfaces (Carretero et al. 2006).

Experience has shown yet that bentonite can decrease the bleeding and clotting time and therefore is suggested as a haemostatic agent. Also, pastes of *healing muds* and of *peloids* made of *bentonite* and spring thermal water or seawater are commonly used in *pelotherapy*.

All the articles referred to disclose important information about properties, applications and functions of clay, clay minerals and clay-based products in human health. However, most of the industrial applications require an industrial processing involving in particular the chemical beneficiation of the natural clay. It is the case of the so-called designed and engineered clay, such as *acid-activated clay* and *organo-clay*, materials actually in progressive and continuous demand. The term "acid-activated clay" has generally been reserved in the industrial literature for partially dissolved bentonites.

Acid-activated bentonite through treatment with both sulphuric and hydrochloric acids has been a standard product for many decades, with a significant market in the decolourizing of vegetable, animal and mineral oils. Usually Ca^{2+}-bentonite is treated with inorganic acids such as sulphuric and hydrochloric acids that remove the Ca cations from particle surfaces and edges, replacing them by monovalent hydrogen ions and leaching out Fe^{3+}, Fe^{2+}, Al^{3+} and Mg^{2+} cations, and as a consequence particle overall negative electric charge, specific surface area and porosity increase (Christidis et al. 1997; Falaras et al. 1999; Jozefacink and Bowanko 2002; Onal and Sarikaya 2007; Carrado and Komadel 2009; Hussini et al. 2011; Komadel and Madejová 2013a, b; Komadel 2016; Dutta 2018).

According to Komadel and Madejová (2013a, b), acid activation is a common chemical modification of clays, usually bentonites, with a hot solution of a mineral acid (typically HCl or H_2SO_4), and it is used for both scientific and industrial purposes. The aim is to obtain partly dissolved material of increased specific surface area, porosity and surface acidity. The product consists partly of the remains of the starting mineral and partly of an amorphous, porous, protonated and hydrated silica phase with a three-dimensional cross-linked framework. Acid activation modifies principal clay properties and thus also their industrial applications.

Onal and Sarikaya (2007) have used acidic aqueous bentonite suspensions heated at 97°C for 6 hours, the acid content being changed from zero to 70% by mass based on the dry bentonite-acid mixture.

Alkali-activated bentonite, more precisely Na-activated bentonite, is the result of the following reaction:

$$\text{Ca}\quad\text{bentonite} + \text{Na}_2\text{CO}_3 \rightarrow \text{CaCO}_3 + \text{Na}\quad\text{bentonite}$$

In nature Na-bentonite is less abundant than Ca-bentonite, and Na-bentonite having more and interesting industrial applications than Ca-bentonite justifies the technological processes of alkaline or alkali activation of Ca-bentonite. One important application of Na-bentonite is in slurry walls, also known as *diaphragm walls*, used in modern construction to prevent the seepage of groundwater, the slurry wall being a trench filled with a thick colloidal mixture of Na-bentonite and water. Na-bentonite, in small amounts of 2–4%, has also an important practical application in ceramics, in particular in the processing of wall tiles and floor tiles which use high-pressing methods of dry powders of kaolin/feldspar mixtures, taking advantage of the clay plastifying and bonding capacity.

Organoclays are organically modified clays or clay minerals by exchanging the original interlayer cations of 2:1 clay minerals, particularly *montmorillonite*, for organic cations, typically quaternary alkylammonium ions, generating organophilic surfaces (Betega de Paiva et al. 2008; He et al. 2014; Guégan 2019). The final characteristics of *organoclays* mainly depend on the type of inorganic layered materials used and the chemical nature of the surfactant for the surface modification.

Organic treatment of some clay types, particularly of smectitic clays, has sparked an explosive interest on a class of materials called polymer-clay nanocomposites (PCNs) utilized for structural reinforcement and mechanical strength, as flame retardants in thermoplastics and bionanocomposites.

Organoclays are also appropriate for the adsorption of organic contaminants such as pesticides, herbicides and pharmaceuticals that are more and more found in the water resource despite wastewater treatments. Claytone APA V and Claytone MPZ V are the trade names of organoclays based on montmorillonite. The corresponding data sheets contain the technical description of products, properties and applications. Claytone APA V, for instance, is an organoclay used in cosmetics, in which it acts as thickening and suspending agent for medium to high polar oil and solvent phases.

Montmorillonite, the most widely known clay mineral of the *smectite group minerals*, and the main constituent of *bentonite* is the most commonly used clay mineral in PCNs (Carrado and Bergaya 2007; Darder and Ruiz-Hitzky 2007; Carrado and Komadel 2009).

As said before, *cationic clay minerals* can be both natural and synthetic, the last having the advantage relative to the first, of homogeneous structural and compositional properties, as well as lower rates of chemical and microbial contamination.

Clay minerals used in pharmaceutical formulations should be highly consistent in terms of particle size, chemistry, water content and free from chemical (heavy metals) and microbial (pathogens) contaminations.

Based on the application, for instance, synthetic cationic-smectite could be modified in order to become enriched in specific metals, Fe, Zn, Co, Cu and Ni. The additives could be organic compounds such as surfactants and polymers that become fixed on the surface, edges or interlayer spaces of clay particles.

The modified clay minerals could be divided in subgroups: clay-drug hybrids, clay-polymer hybrids and organoclays.

Figure 6.18 shows the different types of cationic clay minerals and their applications in various biological systems (Ghadiri et al. 2015).

Clay of the *nanoclay* typology besides important general applications in fields, such as *catalysis* (Garrido-Ramirez et al. 2010; Nagendrappa 2011), food packaging (Azeredo 2009; Majeed et al. 2013); *textile industry* (Floody et al. 2009; Shahidi and Ghoranneviss 2014); *high strength materials with thermal and gas barrier properties* (Liu et al. 2011; Wu et al. 2014; Gamelas and Ferraz 2015); has specific and other rather important applications in fields such as *medicine* (Ambre et al. 2010; Suresh et al. 2010), *cosmetics* (Patel et al. 2006; Carretero and Pozo 2009, 2010) and *pharmacy* (Carretero and Pozo 2009, 2010).

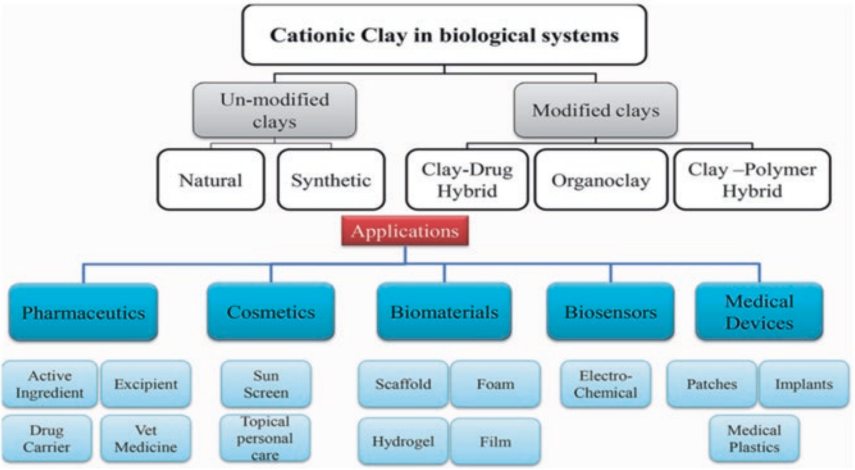


Fig. 6.18 Different types of cationic clay minerals and their applications in various biological systems (*In*: Ghadiri et al. 2015)

Biocomposites are materials composed of biomolecules and inorganic solids, such as clay minerals. The term "biocomposite" was initially introduced by Toyota Central Research Laboratory by the end of 1985, while they secured success in fabrication of *nylon-montmorillonite* clay-based nanocomposites in order to produce a belt cover for car (Kojima et al. 1993a, b).

Very recently, Oliveira et al. (2018) produced an interesting article on "Immobilization of Biomolecules on Natural Clay Minerals for Medical Applications". Indeed, clay minerals combining nanometric particle size with adsorptive capacity, lack of toxicity and biocompatibility are really promising materials to be used as biocomposites able to immobilize biomolecules on their electrically charged surfaces, which are characterized for having positive and negative sites, and as so, high surface reactivity (Ruiz-Hitsky et al. 2015).

Clay minerals can reversibly fix and protect the biomolecules, organic entities of biological origin, such as polysaccharides, lipids, enzymes, amino acids, peptides and nucleic acids. Clay minerals need to undergo modification and functionalization of their particle surfaces before incorporation into polymer matrices to develop polymer-clay nanocomposites.

Nanoclays are clay minerals which particles have a high form or aspect ratio with at least one dimension of the particle in the nanometre range. The purity, electric charge, cation exchange capacity and specific surface area are critical characteristics.

Montmorillonite, *halloysite*, *hectorite* and *saponite* are the most commonly used nanoclays. Montmorillonite after being Na^+-activated to improve its swelling is able to insert organic cations. These cations reduce the surface energy of the clay mineral, making it more organophilic, thus facilitating access between the layers of monomers and polymers with different polarities.

As a consequence of clay minerals' electric charge, in general, they show hydrophilic character turning them incompatible with a wide range of polymer types. However, organophilic clay minerals can be produced by ion exchange with an organic cation. For instance, in *Na^+-montmorillonite*, sodium ions can be exchanged for an amino acid such as 12-aminododecanoic acid (ADA) to turn the clay mineral hydrophobic and therefore more compatible with polymers.

Nanoclay specific surface area is an important factor, since higher surface areas facilitate the interaction clay-polymer. Refining, i.e. going down from micro- to nanoscale, as well as delamination or exfoliation of the platy particles of clay minerals such as *kaolinite* and *montmorillonite* could significantly increase their specific surface areas and consequently the exposure to the polymer matrix. In all applications, nanoclay improves the product quality, costs economy and environment safety (Nazir et al. 2016).

Nanoparticles of other materials are currently available, such as aluminium oxide, copper oxide, iron oxide, titanium dioxide, zinc oxide and calcium carbonate.

Clay minerals are naturally hydrophilic and most polymers are hydrophobic. Hence to render miscible one clay mineral with a hydrophobic polymer, the clay mineral has to be treated with certain organic substances becoming an organoclay that could be employed in biological applications, for instance, for drug delivery or tissue engineering (Lee and Fu 2003; Vasilakos and Tarantili 2012).

Clay is the main constituent of the so-called healing clays and edible clays, and within the *healing clays*, it is the main constituent of most natural peloids and *peloids s.s. (strictu sensu)* particularly of the essentially inorganic peloids used for therapeutic and cosmetic purposes, either applied outdoors in the natural environment, or applied indoors in specialized spas. *Edible clays* and *healing clays* are described in subchapters 7.2 and 7.3 of Chap. 7, respectively.

A particular reference is due yet to the so-called antibacterial clay or killer clay or bactericide clay, a natural clay whose name is grounded on scientific arguments (see subchapter 7.5 of Chap. 7 in this book).

Kaolin and bentonite are special types of clay having unique properties of widespread technological importance and traditional applications such as ceramics (porcelain, earthenware, tableware and sanitary ware), paper coating, plastics, pharmaceuticals, paints and cosmetics. New *kaolin* applications include nano-sized materials for use in the inks of modern printers, nontoxic pesticides in organic farming and polymer composites used in the packaging industry.

In the future, expectations are great in the field of nanocomposites derived from kaolins to improve the rheological, thermal and organic complexation capabilities of products used in engineering and medicine, in the last case to carry and deliver pharmaceuticals by using nanotubes of *halloysite* as a Trojan horse (Schroeder and Erickson 2014).

6.6 Specific Properties of Clay Minerals That Justify Their Interest in Pharmacy, Therapeutics and Cosmetics

Kaolinite, *halloysite*, *montmorillonite*, *beidellite*, *talc*, *sepiolite* and *palygorskite* are the most commonly used clay minerals for medical, pharmaceutical and cosmetic applications, either as active substances or as excipients.

With respect to the clay/human body interaction, clay particles can adsorb and make accessible for incorporation, by ingestion or dermal absorption, either bio-essential elements or toxic elements (e.g. heavy metals). The clay particles may also adsorb and make available for disposal or excretion any potentially toxic elements or toxins that have been ingested or produced by metabolism.

Much of what is discussed in this subchapter is a replica of the information provided in the article entitled "Healing and Edible Clays: A Review of Basic Concepts, Benefits and Risks" recently published by Gomes (2018) in the journal *Environmental Geochemistry and Health*.

The clay and clay mineral properties that justify their use in human health care are the following:

1. Ubiquitary of clay deposits, located on or near the Earth's surface, making its access and extraction simple.
2. Extraordinarily small size of clay minerals (usually less than 2 μm, but down to the nanometre size) and anisometric particle shape diversity (lamellar in most clay minerals, but fibrous, tubular or spherical in others) – both these characteristics are essential conditions to provide the clay with a high specific surface area value (commonly between 10 and 300 $m^2.g^{-1}$), a property that is a determining factor when the clay is used, for example, or in the lining of the stomach and small intestine to alleviating nausea and indigestion, or topical coating and adhesion to the skin, or for localized and controlled delivery and delivery of medicament; however, these characteristics may not be good if the clay, taking into account the small size and shape of its particles, provides toxicity associated with continued inhalation.
3. Clay minerals have a generally negative electric charge, due mainly to structural defects (isomorphous atomic substitutions, atomic omissions, and broken bonds at the edges of the particles); the clay minerals of the *kaolinite group* have a low net electric charge (0.1–0.2), corresponding to a half unit cell; the clay minerals of the *smectite group* have an intermediate liquid electric charge (0.2–0.6), also corresponding to a half unit cell, which is responsible for the expansion of the structure (the degree of expansion depends on the nature and hydration capacity of the intercalation cations, this is positioned in the spaces between structural layers and the degree of humidity of the environment in which the minerals occur) and also responsible for the collapse of the structure in dry environment; the clay minerals of the *illite group* have high net electric charge (0.6–0.9), corresponding to a half cell unit, reason why they do not expand when hydrated; the overall negative charge of the clay minerals being

dependent on the pH of the occurrence environment can be modified (even compensated and neutralized) by the effect of surface coatings, for example, quasi-amorphous or amorphous iron hydroxides of positive electric charge; such modifications will have consequences on relevant clay properties, such as ion exchange, plasticity and rheology.

4. Low hardness and abrasiveness, properties that provide pleasant sensation when a paste of clay comes in contact with the skin and is spread on it.
5. High affinity for water, facilitating the formation of both plastic pastes with adequate fluidity, suitable scattering and adhesion to the skin and stable dispersions/suspensions.
6. High adsorption/absorption capacities, properties that allow the adsorption/absorption of toxins, bacteria and viruses, and their elimination from the skin, making efficient the use of certain types of curative mud/peloid in the treatment of skin conditions such as acne, seborrhoea, eczema and psoriasis, and allowing the use of certain nanotubular clays as is the case of halloysite in the process of controlled release of medicaments at the desired site.
7. Alkaline pH clays can neutralize the gastrointestinal acidity, while clays of acid pH, if similar to the pH of the skin, avoid skin irritations.
8. High cation and anion exchange capacities, properties that promote reversible attachment and exchange of chemical elements/compounds (polar, in particular), for example, or between clay and skin-based facial masks, or incorporation of elements/compounds of medicinal interest.
9. Reduced species of exchangeable elements, such as Fe^{2+} and their oxidation, are responsible for the bactericidal action of certain clays, for example, those known as “French green clays”, which become toxic to microorganisms that are pathogenic to humans.
10. High heat retention capacity and low heat diffusivity, important characteristics for curative mud/peloid coatings, packs and poultices that are applied, either hot (not above 45 °C), or cold, depending on the nature of the affections to deal with; the cooling rate of curative mud/peloid (typically 15–20 min from 45 °C to 37 °C) is conditioned by factors such as global composition and clay texture, nature and quantity of clay minerals, nature and amount of the associated organic substances and the nature of the liquid phase (natural mineral water, spring water, seawater, salt lake water, etc.), the amount of which is also very influential, as a rule, between 40 and 80%.
11. Great diversity of natural colours and possibility of artificial pigmentation, in case the clay presents white colour.

Due to these and other properties, such as dispersibility, hygroscopicity, greasiness, plasticity, thixotropy, chemical inertia and none or negligible toxicity, clay and clay minerals are widely used in the pharmaceutical industry as a lubricant, desiccant, disintegrant, diluent, stabilizer, binder, opacifier and pigment, as well as emulsifier, thickener and as an isotonic and anticaking agent, they can still be used as a flavouring agent and active ingredient carrier.

Clay mineral surface properties are also of paramount importance in medical applications. In the last few decades, some clay minerals, particularly *halloysite*, *montmorillonite*, *sepiolite* and *palygorskite*, based on basic and clinical research, have been considered efficient carriers of active drug molecules providing important applications in the medical industry.

Clay minerals have important roles in drug encapsulation (Delcea et al. 2011;), in drug delivery systems, in the formation of antimicrobial surfaces (Babu et al. 2018), in the release of active substances (da Silva et al. 2016) and in drug efficiency (Ambrogi et al. 2014). Some clay minerals, such as *montmorillonite*, are efficient sorbents of various types of drugs, such as antibiotics, photosensitizers (Donauerová et al. 2015) or disinfectants. *Organoclays* such as *montmorillonite* treated with quaternary ammonium salts have been tested as antimicrobial and disinfection agents (Hong and Rhim 2008; Bragg et al. 2014; Yuen et al. 2015).

Among the main healing properties of clay and clay minerals are the following: antacid, gastrointestinal protector, antidiarrhoeal, laxative, homeostatic, emetic and antianaemic. Besides the bibliographic references mentioned in the chapter's body, some others have provided relevant information used in the preparation of this chapter, such as: Abad et al. (2001), Al-Ani & Sarapaa (2008), Bailey (1977), Bailey (1981), Bergaya & Lagaly (2001), Bergaya & Lagaly (2006), Brigatti et al. (2011), Bujdáková et al. (2018), Cervini-Silva et al. (2015), Chang et al. (2009), Choy & Park (2004), Churchman & Lowe (2012), Clauer & Chaudhuri (1995), Cuadros et al. (2013), Cuadros (2013), Direcção-Geral de Geologia e Minas, Ministério da Indústria e Energia (1985), Drits & Zviagina (2009), Fiore et al. (2009), Galán (2003), Galán & Ferrell (2006), Galán & Aparício (2013), Gomes & Rautureau (2013), Gomes et al. (2015), Guggenheim (2011), Heller-Kalai (2013), Hu & Yang (2013), Keller (1970), Keller (1976), Keller (2000), Låg (1990), Limpitlaw (2004), Merriman (2005), Merriman (2006), Mitchell & Vincent (1997), Moore & Reynolds (1997), Murray et al. (1993), Murray (2000), Nagasawa & Moro (1987), Ponto & Berg (1918), Pozo & Calvo (2018), Savechenkov (1862), Savic et al. (2014), Suárez & Garcia-Romero (2006), Tateo & Summa (2007), Thompson (1914), Weiss & Range (1970), and Wesley (2014).

References

Abad I (2003) Physical meaning and application of the illite Kubler index: measuring reaction progress in low-grade metamorphism. Seminarios SEM (Sociedad Española de Mineralogia) 3, 53, 12 pp

Abad I, Mata MP, Nieto F, Velilla N (2001) The phyllosilicates in diagenetic-metamorhic rocks of the south Portuguese zone, southwestern of Portugal. Can Mineral 39:1571–1589

Adamo P, Violante P, Wilson MJ (2001) Tubular and spheroidal halloysite in pyroclastic deposits in the area of Roccamonfina volcano, Southern Italy. Geoderma 99:295–316

Al-Ani T, Sarapaa O (2008) Clay and clay mineralogy: physical-chemical properties and industrial uses

Aguzzi C, Cerezo P, Viseras C, Caramella C (2007) The use of clays as drug delivery systems: possibilities and limitations. Appl Clay Sci 36:22–36

Aguzzi C, Sandri G, Derezo P, Carazo E, Viseras C (2016) Health medical application of tubular clay minerals. In: Yuan P, Thill A, Bergaya F (eds) Nanosized tubular clay minerals., Elsevier

Ambre AH, Katti KS, Katti DR (2010) Nanoclay based composite scaffolds for bone tissue engineering applications. J Nanotechnol Eng Med 1:031013

Ambrogi V, Nocchetti M, Latterini L (2014) Promethazine-montmorillonite inclusion complex to enhance drug photostability. Langmuir 30:14612–14620

Askenasy PE, Dixon JB, Mckee TR (1973) Spheroidal halloysite in Guatemalan soil. Soil Sci Soc Am Proc 37:799–803

Aufreiter S, Hancock RGV, Mahaney WC, Stambolic-Robb A, Sanmugadas K (1997) Geochemistry and mineralogy of soils eaten by humans. Int J Food Sci Nutr 48:293–305

Awad M, López-Galindo A, Setti M, El-Rahmany MM, Viseras C (2017) Kaolinite in pharmaceuticals and biomedicine. Int J Pharm 533:34–48

Azeredo HMCD (2009) Nanocomposites for food packaging applications. Food Res Int 42:1240–1253

Babu SS, Kalarikkal N, Thomas S, Radhakrishnam EK (2018) Enhanced antimicrobial performance of cloisite 30B/poly (caprolactone) over cloisite 30B/poly (lctic acid) as evidenced by structural features. Appl Clay Sci 153:198–204

Bailey SW (1977) Report of the IMA-IUCr Joint Committee on Nomenclature. Am Mineral 62:411–415

Bailey SW (1980a) Structure of layer silicates. In: Brindley GW, Brown G (eds) Crystal structures of clay minerals and their X-ray identification. Mineralogical Society, London, pp 1–123

Bailey SW (1980b) Summary of recommendations of AIPEA Nomenclature Committee for 1977-1978. Clays Clay Miner 28:73–78.; Clay Miner 15: 85–93

Bailey SW (1981) A system of nomenclature for regular interstratifications. Can Mineral 19:651–655

Bailey SW (1989) Report of the AIPEA Nomenclature Committee. AIPEA Newslett 26:17–18

Bailey SW, Brindley GW, Johns WD, Martin RT, Ross M (1971a) Summary of national and international recommendations on clay minerals nomenclature, 1969-1970. Clays Clay Miner 19:129–132

Bailey SW, Brindley GW, Johns WD, Martin RT, Ross M (1971b) Clay Mineral Society, Report of Nomenclature Committee 1969-1970. Clays Clay Miner 19:132–133

Bailey SW, Brindley GW, Kodama H, Martin RT (1979) Report of Clay Minerals Society Nomenclature Committee for 1977-1978. Clays Clay Miner 27:238–239

Bailey SW, Alietti A, Formoso MLL, Konta J, Koster HM, Mackenzie RC, Morgan DJ, Mumpton FA, Nagasawa K, Paquet H, Raussell-Colom JA, Zvyagin BB (1986) Report of the AIPEA Nomenclature Committee, AIPEA Newslett 22(Supplement February)

Bardossy G (1982) Karst Bauxites: Bauxite deposits on carbonate rocks. In: Developments in economic geology, vol 14. Elsevier Science, 441 pp

Bergaya F, Lagaly G (2001) Surface modification of clay minerals. Appl Clay Sci 19(1-6):1–3

Bergaya F, Lagaly G (2006) Chapter 7: Introduction to pure clay minerals. In: Bergaya F, BKG T, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1. Elsevier, Amsterdam, pp 717–741

Bergaya F, Lagaly G (2007) Clay minerals properties responsible for clay-based polymer nanocomposite (CPN) performance. In: Carrado KA, Bergaya F (eds) Clay Based Polymer Nanocomposites (CPN). CMS workshop lectures, vol 15, 61–97

Bergaya F, Lagaly G, Beneke K (2006) Chapter 15: History of clay science: a young discipline. In: Bergaya F, BKG T, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1, pp 1163–1181

Bergaya F, Jaber M, Lambert JF (2011) Chapter 2: Organophilic clay minerals. In: Galimberti M (ed) Rubber clay nanocomposites, Science, technology, and applications. Wiley, Chichester, pp 45–86

Bergaya F, Lagaly G, Vayer M (2013) Chapter 2.11: Cation and anion exchange. Developments in clay science, vol 5B, pp 333–359

Betega de Paiva L, Morales AR, Valenzuela Diaz FR (2008) Organoclays: properties, preparation and applications. Appl Clay Sci 42(1–2):8–24

Bhattacharyya KG, SenGupta S, Sarma GK (2014) Interactions of the dye, rhodamine B with kaolinite and montmorillonite in water. Appl Clay Sci 99:7–17

Bovey J, Kooli F, Jones W (1996) Preparation and characterization of Ti-pillared acid activated clay catalyst. Clay Miner 31:501–506

Bradley WF (1940) The structural scheme of attapulgite. Am Miner 25:405–413

Bragg R, Jansen A, Coetzee M, van der Westhuizen W, Boucher C (2014) Bacterial resistance to quaternary ammonium compounds (QAC) disinfectants. Adv Exp Med Biol 808:1–13

Brauner K, Preissinger A (1956) Struktur und entstehung des Sepioliths. Min Petr Mitteil 6:120–140

Brigatti F, Guggenheim S (2002) Mica structure chemistry and the influence of pressure, temperature, and solid solution on atomistic models. Rev Mineral Geochem 46(1):1–97

Brigatti MF, Galán E, Theng BKG (2006) Structures and mineralogy of clay minerals. In: Bergaya F, Theng BKG, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1. Elsevier, Amsterdam, pp 19–86

Brigatti MF, Malferrari D, Laurora A, Elmi C (2011) Structure and mineralogy of layer silicates: recent perspectives and new trends. In: Brigatti MF, Mottana A (eds) Layered mineral structures and their applications in advanced technologies, EMU notes in mineralogy, vol 11. Mineralogical Society, London, pp 1–71

Brigatti MF, Galán E, Theng BKG (2013) Structure and mineralogy of clay minerals. Developments in clay science, vol 5A, Elsevier, pp 21–81

Brindley GW (1959) X-ray and electron diffraction data for sepiolite. Am Miner 44(5–6):495–500

Brindley GW, Brown G (1980) Crystal structures of clay minerals and their X-Ray identification. Mineralogical Society Monograph, n°5, London

Brindley GW, Pedro G (1970) Report of the AIPEA nomenclature committee. AIPEA Newslett 7:8–13

Brindley GW, Pedro G (1976) Meeting of the Nomenclature Committee of AIPEA, Mexico City, July 21, 1975. AIPEA Newslett 12:5–6

Brunet de Courssou L (2002) 5th WHO Advisory Group meeting on Buruli ulcer. Study Group Report on Buruli Ulcer Treatment with Clay, Geneva, Switzerland

Bujdáková H, Bujdáková V, Májeková-Koscova H, Gaálová B, Bizovshá V, Bohác P, Bujdák J (2018) Antimicrobial activity of organoclays based on quaternary alkylammonium and alkylphosphonium surfactants and montmorillonite. Appl Clay Sci 158:21–28

Caillère S, Hénin S, Esquevin J (1953) Synthèses à basse température de phyllite ferrifère. Comptes Rendus de l'Académie des Sciences, Paris vol 237, pp 1724–1726

Caillère S, Oberlin A, Hénin S (1954) Étude au microscope électronique de quelques silicates phylliteux obtenus par synthèses à basse températue. Clay Miner Bull 2:146–156

Caillère S, Hénin S, Esquevin J (1955) Synthèses à basse température de quelque minéraux ferrifère (silicates et oxydes). Bull de la Société Française de Minéralogie et Cristallographie 78:227–241

Caillère S, Hénin S, Rautureau M (1982) Minéralogie des Argiles. I: Structure et Propriétés Physico-Chimiques, 184 pp, II: Classification et Nomenclature. Masson, Paris, 189 pp

Caillère S, Hénin S, Rautureau M (1989) Les Argiles. Septima (ed.), Paris, 126 pp

Calvo JP, Pozo M (2013) Geology of magnesium clays in sedimentary and non-sedimentary environments. In: Pozo M, Galán E (eds) Magnesium clays: characterization, origin and applications. Aipea Educational Series, vol 2, 63–123–174

Carrado KA, Bergaya F (2007) Clay-Based polymer nano-composites. CMS workshop Lectures Series, vol 15, Clay Minerals Society, Chantilly, Virginia, 278 pp

Carrado KA, Komadel P (2009) Acid activation of bentonites and polymer-clay nano-composites. Elements 5:111–115

Carrado KA, Decarreau A, Petit S, Bergaya F, Lagaly G (2006) Chapter 4: Synthetic clay minerals and purification of natural clays. Developments in clay science 1, pp 115–139

Carretero MI (2002) Clay minerals and their beneficial effects upon human health: a review. Appl Clay Sci 21(3–4):155–163

Carretero MI, Pozo M (2007) Mineralogía aplicada: salud y medio ambiente. Thomson, Madrid, 464 pp

Carretero MI, Pozo M (2009) Clay and non-clay minerals in the pharmaceutical industry: Part I – Excipients and medical applications. Appl Clay Sci 46:73–80

Carretero MI, Pozo M (2010) Clay and non-clay minerals in the pharmaceutical and cosmetics industry: part II – Active ingredients. Applied Clay Science 47:171–181

Carretero MI, Gomes CSF, Tateo F (2006) Clays and human health. In: Bergaya F, Theng BKG, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1. Elsevier, Amsterdam, pp 717–741

Carretero MI, Pozo M, Martin-Rubi JA, Pozo E, Maraver F (2010) Mobility of elements in interaction between artificial sweat and peloids used in Spanish spa. Appl Clay Sci 48(3):506–515

Carretero MI, Gomes CSF, Tateo F (2013) Chapter 5.5: Clays, drugs and human health. In: Bergaya F, Lagaly G (eds) Handbook of clay science. Part B. Techniques and applications, 2nd edn. Elsevier, pp 711–764

Carroll D (1979) Clay minerals: a guide to their x-ray identification. Geological Society of America special paper 126, 80 pp

Cavallaro G, Lazzara G, Massaro M, Milioto S, Noto R, Parisi F, Riela S (2015) Biocompatible poly (N-isopropylacrylamide)-nanotubes for thermoresponsive curcumin release. J Phys Chem C 119:8944–8951

Cervini-Silva J, Nieto-Camacho A, Gómez-Vidales V, Kaufhold S, Theng BKG (2015) The anti-inflammatory activity of natural allophane. Appl Clay Sci 105–106:48–51

Chamley H (1989) Clay sedimentology. Springer, Berlin, 623 pp

Chang PH, Li Z, Yu TL, Munkhbayer S, Kuo TH, Hung YC, Jean JS, Lin KH (2009) Sorptive removal of tetracycline from water by palygorskite. J Hazard Mater 165:148–155

Chen T, Peng CQ (1990) A mineralogical investigation on synthetized Mg–Si-mica. Acta Mineral Sin 10(2):127–131

Chen P-Y, Lin M-L, Zheng Z (1997) On the origin of the name kaolin and the kaolin deposits of the Kauling and Dazhou areas, Kiangsi, China. Appl Clay Sci 12:1–25

Cheng H, Zhou Y, Liu Q (2019) Chapter 6: Kaolinite nanomaterials: preparation, properties and fundamental applications. In: Wang A, Wang W (eds) Nanomaterials from clay minerals: a new approach to green functional materials. Elsevier, pp 285–334

Choy J-H, Park M (2004) Cationic and anionic clays for biological applications. Interface Sci Technol 1:403–424

Christidis GE (2011) Industrial clays. In: Christidis GE (ed) Advances in the characterization of industrial minerals, EMU notes in mineralogy, vol 9. Mineralogical Society, London, pp 341–414

Christidis GE (2013) Chapter 4.1: Assessment of industrial clays. Developments in clay science, vol 5B. Elsevier, pp 425–449

Christidis GE, Huff W (2009) Geological aspects and genesis of bentonites. Elements 5(2):93–98

Christidis GE, Scott PW, Dunham AC (1997) Acid activation and bleaching capacity of bentonites from the islands of Milos and Chios, Aegean, Greece. Appl Clay Sci 12:329–347

Christidis GE, Aldana C, Chryssikos G, Gionis V, Kalo H, Stoter M, Breu J, Robert J-L (2018) The nature of laponite: pure hectorite or a mixture of different trioctahedral phases? Minerals 8:314

Churchman GJ, Lowe DJ (2012) Alteration, formation, and occurrence of minerals in soils. In: Huang PM, Sumner ME (eds) Handbook of soil sciences, 2nd edn, vol 1, Properties and processes 20. CRC Press (Taylor and Francis), Boca Raton, pp 1.20.72

Churchman GJ, Pasbakhsh P (2015) Current trends in research and application of natural mineral nanotubes. In: Pasbakhsh P, Churchman GJ (eds) Natural mineral nanotubes. Apple Academic Press, Oakville, pp 481–488

Churchman GJ, Aldridge LP, Carr RM (1972) Clays Clay Miner 20:241

Churchman GJ, Pasbakhsh P, Lowe DJ, Theng BKG (2016) Unique but diverse: some observations on the formation, structure and morphology of halloysite. Clay Miner 51:395–416

Clauer N, Chaudhuri S (1995) Chapter 1: an introduction to clay minerals and isotope geochemistry. In: Clays in crustal environments: isotope dating and tracing. Springer

Combes PJ, Bardossy G (1995) Chapter 4D: Geodynamics of bauxites in The Tethys Ocean. In: Nairn AEM et al (eds) The ocean basins and margins. vol 8: The Tethys Ocean. Plenum Press, pp 347–365

Cravero F, Fernández L, Marfil S, Sánchez M, Maiza P, Martínez A (2016) Spheroidal halloysites from Patagonia, Argentina: Some aspects of their formation and applications. Appl Clay Sci 131:48–58

Cuadros J (2013) Crystal-chemistry of mixed-layer clays. In: Fiore S, Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA Educational Series, Publication n° 1, 2nd edn, pp 11–34. ISBN: 978-88-7522-046-4

Cuadros J, Fiore S, Huertas FJ (2013) Introduction to mixed-layer clay minerals. In: Fiore S, Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA Educational Series, Publication n° 1, 2nd edn, pp 1–10. ISBN: 978-88-7522-046-4

Cunningham MJ, Lowe DJ, Wyatt JB, Moon VG, Churchman GJ (2016) Discovery of halloysite books in altered silicic Quaternary tephras, Northern New Zealand. Clay Miner 51:351–372

Dal Bosco SM, Jimenez RS, Vignado C, Fontana J, Geraldo B, Figueiredo FCA, Mandelli D, Carvalho WA (2006) Removal of Mn(II) and Cd(II) from wastewaters by natural and modified clays. Adsorption 12:133–146

Darder M, Ruiz-Hitzky E (2007) Bionanocomposites based on clay minerals. In: Carrado K, Bergaya F (eds) CMS workshop lectures series, vol 15. Clay Minerals Society, Chantilly, Virginia, pp 231–256

De Lapparent J (1935) An essential constituent of fuller's earth. Compt Rendue 201:481–483

De Vos P (2010) European material medica in historical texts: Longevity of a tradition and implications for future use. J Ethnopharmacol 132:28–47

Delcea M, Mohwald H, Skirtach AG (2011) Stimuli-responsive LbL capsules and nanoshells for drug delivery. Adv Drug Deliv Rev 63:730–747

Detellier C, Schoonheydt RA (2014) From platy to nanorolls. Elements 10:201–206

Direcção-Geral de Geologia e Minas, Ministério da Indústria e Energia (1985) Catálogo das Argilas Portuguesas Utilizadas na Indústria Cerâmica, 175 pp

Donauerová A, Bujdák J, Smolinská M, Bujdáková H (2015) Photophysical and antibacterial properties of complex systems based on smectite, a cationic surfactant and methylene blue. J Photochem Photobiol B 151:135–141

Dondi M, Chiara Z, Raimondo M (2014) Clays and bodies for ceramic tiles: reappraisal and technological classification. Appl Clay Sci 96:91–109

Drits VA, Alexandrova VA (1966) The crystallochemical nature of palygorskites. Zap Vses Miner Obshch 95:551–560

Drits VA, Zviagina BB (2009) Trans-vacant and Cis-vacant 2:1 layer-silicates: structural features, identification and occurrence. Clay Clay Miner 57(4):405–415

Droy Lefaix MT, Tateo F (2006) Clays and clay minerals as drugs. In: Bergaya F, Theng BKG, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1. Elsevier, Amsterdam, pp 743–753

Dutta DK (2018) Acid-modified nanoporous montmorillonite. In: Schoonheydt R, Johnston CT, Bergaya F (eds) Developments in clay science, vol 9. Elsevier, pp 289–329

Emiel JM, Hensen SB (2002) Why clay swell. J Phys Chem B 106(49):12664–12667

Emmerich K (2013) Chapter 2.13: Full characterization of smectites. In: Developments in clay science, vol 5B. Elsevier, Amsterdam, pp 381–404

Emmerich K, Wolters F, Kahr G, Lagaly G (2009) Clay profiling: The classification of montmorillonites. Clays Clay Miner 57:104–114

Fakhrullin RF, Lvov YM (2016) Halloysite clay nanotubes for tissue engineering. Nanomedicine 11:2243–2246

Falaras P, Kovanis I, Lezou F, Seiragakis G (1999) Cottonseed oil bleaching by acid-activated montmorillonite. Clay Miner 34:221–232

Ferrell RE, Aparício P, Forsman J (2013) Interstratified clay minerals in the weathering environment. In: Fiore S, Javier Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance AIPEA educational series, Pub. No. 1, pp 35–52

Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M (2011) Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int 31(1):1–8

Fiore S, Quadros J, Huertas FJ (eds) (2009/2013) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA educational series, Publication n°1, 175 pp, 1st edn (2009), 2nd edn (2013). ISBN: 978-88-7522-046-4

Floody MC, Theng B, Reyes P, Mora M (2009) Natural nanoclays: applications and future trends – a Chilean perspective. Clay Miner 44:161–176

Galán E (1996) Properties and applications of Palygorskite-Sepiolite clays. Clay Miner 31:443–453

Galán E (ed) (2003) Mineralogia Aplicada. Sintesis, Madrid

Galán E (2006) Chapter 14: Genesis of clay minerals: geological environments for clay formation. In: Bergaya F, Theng BKG, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1, pp 1129–1162

Galán E, Aparício P (2013) Methodology for the identification and characterization of magnesium clays. In: Pozo M, Galán E (eds) Magnesium clays: characterization, origin and applications, vol 2. AIPEA educational series, pp 63–121

Galán E, Carretero I (1999) A new approach to compositional limits for sepiolite and palygorskite. Clays Clay Miner 47:399–409

Galán E, Ferrell RE (2006) Chapter 3: genesis of clay minerals. Developments in clay science, vol 5, pp 83–126

Gamelas JAF, Ferraz E (2015) Composite films based on nanocellulose and nanoclay minerals as high strength materials with gas barrier capabilities: key points and challenges. BioRes 10(4):6310–6313

Garcia-Romero E, Suárez M (2010) On the chemical composition of sepiolite and palygorskite. Clays Clay Miner 58(1):1–20

Garrido-Ramirez E, Theng B, Mora M (2010) Clays and oxide minerals as catalysts and nanocatalysts in Fenton-like reactions: a review. Appl Clay Sci 47:182–192

Ghadiri M, Chrzanowski W, Rohanizadeh R (2015) Biomedical applications of cationic clay minerals. RSC Adv 5:37. https://doi.org/10.1039/C4RA16945J

Gomes CSF (1966a) On the hyperaluminous clays from Andorinha-Cantanhede (Portugal). Memórias e Notícias do Museu Mineralógico e Geológico da Universidade de Coimbra 60:55–57

Gomes CSF (1966b) Electron-optical data of authigenic anatase, hematite and goethite from a Portuguese clay. Memórias e Notícias do Museu Mineralógico e Geológico da Universidade de Coimbra 61:81–82

Gomes CSF (1968) On a Sr and Al basic phosphate-sulphate close to svanbergite occurring in Portuguese bauxitic clay. Memórias e Notícias do Museu Mineralógico e Geológico da Universidade de Coimbra 66:3–13

Gomes CSF (1988) Argilas: O que são e para que servem. Fundação Calouste Gulbenkian (editor), Lisboa, 457 pp

Gomes CSF (1992) Occurrence of ferriferous sepiolite in the gabbro quarry of Ribamar, Ericeira (Portugal). Actas del Congreso Geológico de España y VIII Congreso Ltinoamericano de geologia. Tomo 3, pp 134–137

Gomes CSF (2002) Argilas: Aplicações na Indústria. Edição do autor. ISBN: 972-8684-12-6, 338 pp

Gomes CSF (2015) In pelotherapy what is more important, the peloid solid phase or the peloid liquid phase? Balnea 10:125–142

Gomes CSF (2018) Healing and edible clays: A review of basic concepts, benefits and risks. Environ Geochem Health 40:1739–1765. https://doi.org/10.1007/s10653-016-9903-4

Gomes CSF, Rautureau M (2013) The role of clay and clay minerals in peloid properties. In: Nunes J, Gomes C, Silva J. (eds) Livro de Actas do III Congresso Iberoamericano de Peloides, Ponta Delgada, São Miguel, Açores, pp 86–93

Gomes CSF, Silva JBP (2007) Minerals and clay minerals in medical geology. Appl Clay Sci 36:4–21

Gomes CSF, Hernandez R, Sequeira MC (2009) Characterization of clays used for medicinal purposes in the Archipelago of Cape Verde. Geochimica Brasiliensis 22(3):315–331

Gomes CSF, Carretero MI, Pozo M, Maraver F, Cantista P, Armijo F, Legido JL, Teixeira F, Rautureau M, Delgado R (2013a) Peloids and pelotherapy: historical evolution, classification and glossary. Appl Clay Sci 75–76:28–38

Gomes A, Simões M, Cavaleiro J, Gomes J, Gomes C, Silva J, Santos D, Pontes A (2013b) Study of the organic constituents of the volcanic mud from the "blue pool" of the Balneário da Coroa, São Miguel Island, Azores, Portugal. In: Nunes J, Gomes C, Silva J (eds) Livro de Actas do III Congresso Iberoamericano de Peloides. Ponta Delgada, São Miguel, Açores, pp 332–339

Gomes CSF, Silva JBP, Gomes JHC (2015) Natural peloids versus designed and engineered peloids. Bol Soc Esp Hidrol Méd 30(1):15–36

Grim RE (1953) Clay mineralogy. McGraw-Hill, New York, 384 pp

Grim RE (1962) Applied clay mineralogy. McGraw-Hill, New York, 422 pp

Grim RE (1968) Clay mineralogy. McGraw-Hill, New York, 569 pp

Grim R, Guven N (1978) Bentonite: geology, clay mineralogy, properties and users, 1978. Elsevier Science Publishing, New York

Guégan R (2019) Organoclay applications and limits in the environment. Comptes Rendus Chimie 22:132–141

Guggenheim S (2011) An overview of order/disorder in hydrous phyllosilicates. In: Brigatti MF, Mottana A (eds) Layered mineral structures and their applications in advanced technologies, EMU notes in mineralogy, vol 11, pp 72–121

Guggenheim S (2013) Introduction to Mg-rich clay minerals: structure and composition. In: Pozo M, Galán E (eds) Magnesium clays: characterization, origin and applications, AIPEA educational series, vol 2, pp 1–62

Guggenheim S, Krekeler MPS (2011) The structure and microtextures of the palygorskite-sepiolite group minerals. Chapter 1, 3–32 pp of Volume 3 "Developments in Palygorskite-Sepiolite Research: A new outlook on these nanomaterials" (eds. Galan E, Singer A) of "Developments in clay science series", Elsevier

Guggenheim S, Martin RT (1995) Definition of clay and clay mineral: joint report of the nomenclature and CMS nomenclature committees. Clays Clay Miner 43(2): 255–256. Clay Miner 30: 257–259

Guggenheim S, Alietti A, Drits VA, Formoso MLL, Galán E, Koster HM, Paquet H, Wanatabe T, Bain DC, Hundnall WH (1997) Report of the AIPEA Nomenclature Committee for 1996. Clays Clay Miner 45: 298–300. Clay Miner 32: 493–496

Guggenheim S, Bain DC, Bergaya F, Brigatti MF, Drits V, Eberl DD, Formoso MLL, Galán E, Merriman RJ, Peacor DR, Stanjek H, Wanatabe T (2002) Report of AIPEA Nomenclature Committee for 2001: order-disorder, and crystallinity in Phyllosilicates and the use of the crystallinity index. Clays Clay Miner 50: 406–409. Clay Miner 37: 389–393

Guggenheim S, Adams JM, Bain D, Bergaya F, Brigatti MF, Drits V, Formoso MLL, Galán E, Kogure T, Stanjek H (2006) Summary of the recommendations of nomenclature committees relevant to clay mineralogy. Report of the Association Internationale pour l'Étude des Argiles (AIPEA). Clay Miner 41(4):863–877

Hanif M, Jabbar F, Sharif S, Abbas G, Farooq A, Aziz M (2016) Halloysite nanotubes as a new drug-delivery system: A review. Clay Miner 51:469–477

Harsh J (2000) Poorly crystalline aluminosilicate clays. In: Sumner ME (ed) Handbook of soil science. CRC Press, Boca Raton, pp 169–182

Harvey CC, Lagaly G (2013) Industrial applications. Developments in clay science, vol 5B. https://doi.org/10.1016/B978-0-08-098259-5.00018-4

Haydel SE, Remineh CM, Williams LB (2008) Broad-spectrum in vitro antibacterial activities of clay minerals against antibiotic-susceptible and antibiotic-resistant bacterial pathogens. J Antimicrob Chemother

Hazen RM et al (2013) Clay mineral evolution. Am Mineral 98:2007–2009

He H, Ma L, Zhu J, Frost RL, Theng BKG, Bergaya F (2014) Synthesis of organoclays: A critical review and some unresolved issues. Appl Clay Sci 100:22–28

Heller-Kalai L (2013) Thermally modified clay minerals. In: Bergaya F, Lagaly G (eds) Handbook of clay science, 2nd edn, vol 5A, Fundamentals, 10.2, pp 411–434

Hillier S, Brydson R, Delbos E, Fraser A, Gray N, Pendlowski H, Phillips I, Robertson J, Wilson I (2016) Correlations among the mineralogical and physical properties of halloysite nanotubes (HNTs). Clay Miner 51:325–350

Hong SI, Rhim JW (2008) Antimicrobial activity of organically modified nano-clays. J Nanosci Nanotechnol 8:5818–5824

Hu P, Yang H (2013) Insight into the physicochemical aspects of kaolins with different morphologies. Appl Clay Sci 47:58–65

Hussini F, Aroua MK, Daud WMAW (2011) Textural characteristics, surface chemistry and activation of bleaching earth: a review. Chem Eng J 170:90–106

Ismadji S, Soetaredjo FE, Ayucitra A (2015) Chapter 2: Natural clay minerals as environmental cleaning agents. In: Clay materials for environmental remediation. SpringerBriefs in Green chemistry for sustainability. https://doi.org/10.1007/978-3-319-16712-1-2

Jaber M, Komarneni S, Zhou C (2013) Synthesis of clay minerals. In: Bergaya F, Lagaly G (eds) Handbook of clay science, 2nd edn. Elsevier, Amsterdam, pp 223–240

Jackson ML (1956) Soil chemical analysis and soil chemical analysis course

Jepson WB (1984) Kaolins: their properties and uses. Philos Trans R Soc Lond A311:411–432

Johnston CT (1996) Sorption of organic compounds on clay minerals: a surface functional group approach. In: Sawhney L (ed) Organic pollutants in the environment. CMS workshop lectures. The Clay Minerals Society, pp 2–44

Johnston CT (2010) Probing the nanoscale architecture of clay minerals. Clay Minerals 45:245–279

Johnston CT, Elzea Kogel J, Bish DL, Kogure T, Murray H (2008) Low-temperature FTIR study of kaolin-group minerals. Clays Clay Miner 56:470–485

Jozefacink G, Bowanko G (2002) Effects of acid and alkali treatments on surface areas and adsorption energies of selected minerals. Clays Clay Miner 50(6):771–783

Karakaya MC, Karakaya N, Sarioglan S, Koral M (2010) Some properties of thermal muds of some Spas in Turkey. Appl Clay Sci 48:531–537

Keller WD (1970) Environmental aspects of clay minerals. J Sed Petrol 40:788–813

Keller WD (1976) Scan electron micrographs of kaolins collected from diverse environments of origin. Clays Clay Miner 24:107–113

Keller EA (2000) Environmental geology, 8th edn. Prentice Hall, Upper Saddle River

Kelly HM, Deasy PB, Ziaka E, Claffey N (2004) Formulation and preliminary in vivo dog studies of a novel drug. Int J Pharm 274(1-2):167–183

Kendall T (1996) Smectite clays. In: Kendal T (ed) Industrial clays. Industrial minerals information, London, pp 1–12

Khan A, Afzal S, Mustafa H, Qumreen M (2018) Data article for adsorption of chemically activated fuller's earth and rice husk for removal of drimarine reactive red dye. Data in brief 21. Elsevier, pp 189–200

Khurana S, Kaur S, Kaur H, Khurana RK (2015) Multifaceted role of clay minerals in pharmaceuticals. Future Science OA 1 (3), Special report, FSO6

Kikouama OJR, Baldé L (2010) From edible clay to clay-containing formulations for optimization of the oral delivery of some trace elements: a review. Int J Food Sci Nutr 61(8):1–21

Kikouama OJR, Konan KL, Katty JA, Bonnet JP, Baldé L, Yagoubi N (2009) Physicochemical characterization of edible clays and release of trace elements. Appl Clay Sci 43(1):135–141

Kingery WD, Bowen HK, Uhlmann DR (1976) Introduction to ceramics, 2nd edn. Wiley, New York

Kirkman JH (1981) Morphology and structure of halloysite in New Zealand tephras. Clays Clay Miner 29:1–9

Kloprogge JT, Komarneni S, Amonette JE (1999) Clays Clay Miner 47(5):529–554

Kojima Y, Usuki A, Kawasumi M, Okada A, Fukushima Y, Kurauchi T, Kamigaito O (1993a) Mechanical properties of nylon 6-clay hybrid. J Mater Res 8:1185–1189

Kojima Y, Usuki A, Kawasumi M, Okada A, Fukushima Y, Kurauchi T, Kamigaito O (1993b) Sorption of water in nylon 6-clay hybrid. J Appl Polym Sci 49:1259–1264

Komadel P (2003) Chemically modified smectites. Clay Miner 38:127–138

Komadel P (2016) Acid activated Clays: Materials in continuous demand. Appl Clay Sci 131:84–99

Komadel P, Madejová J (2013a) Chapter 10.1: Acid activation of clay minerals. Developments in clay science, pp 385–409

Komadel P, Madejová J (2013b) Identification and characterization of interstratified clay minerals with spectroscopic and other classical methods. In: Fiore S, Javier Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA educational series. Publication no. 1, pp 89–114

Kübler B (1964) Les argiles, indicateurs de métamorphisme. Rev Inst Français du Pétrole 19:1093–1112

Kübler B (1968) Evaluation quantitative du métamorphism par la cristallinité de l'illite. Bulletin Centre de Recherche Pau-SNPA 2:385–397

Låg J (1990) General survey of geomedicine. In: Lag J (ed) Geomedicine. CRC Press, Boca Raton, pp 1–24

Laird DA (2006) Influence of layer-charge on swelling of Smectites. Appl Clay Sci 34:74–87

Lee WF, Fu YT (2003) Effect of montmorillonite on the swelling behavior and drug release behavior of nanocomposite hydrogels. J Appl Polymer Sci 89:3652–3660

Leroux F, Besse J-P (2001) Polymer interleaved layered double hydroxides: A new emerging class of nanocomposites. Chem Mater 13(10):3507–3515

Levis SR, Deasy PB (2003) Use of coated microtubular halloysite for the sustained release of diltiazem hydrochloride and propanolol hydrochloride. Int J Pharm 253(1–2):145–157

Limpitlaw UG (2004) The medical use of minerals, rocks and fossils. In: Proceedings of the Geological Society of America, annual meeting abstract 48-5, v36 (5), p 130

Liu M, Jia Z, Jia D, Zhou C (2011) Recent advance in research on halloysite nanotubes-polymer nanocomposite. Prog Polym Sci 39:1498–1525

López-Galindo A, Viseras C, Cerezo P (2007) Compositional, technical and safety specifications of clays to be used as pharmaceutical and cosmetic products. Appl Clay Sci 36:51–63

López-Galindo A, Viseras C, Aguzzi C, Cerezo P (2011) Chapter 13: Pharmaceutical and cosmetic uses of fibrous clays, Advances in the crystal chemistry of sepiolite and palygorskite. In: Galán E, Singer A (eds) Developments in palygorskite-sepiolite research. Developments in clay science, vol 3, pp 290–324. Elsevier

Lvov YM (2008) Bio-inorganic hybrid nanomaterials (eds. Ruiz-Hitzky E, Ariga K, Lvov YM). Wiley, Weinheim

Lvov YM, Schchukin DG, Mohwald H, Price RR (2008) Halloysite clay nanotubes for controlled release of protective agents. ACS Nano 2(5):814–820

Lvov YM, Devilliers MM, Fakhrullin RF (2016) The application of halloysite tubule nanoclay in drug delivery. Expert Opin Drug Deliv 13:977–986

Ma'or Z, Henis Y, Along Y, Orlov E, Sorensen KB, Oren A (2006) Antimicrobial properties of Dead Sea black mineral mud. Int J Dermatol 45:504–511

Majeed K, Jawaid M, Hassan A, Abu Bakar A, Abdul Khalil HPS, Salema AA, Inuwa I (2013) Potential Materials for food packaging from nanoclay/natural fibres filled hybrid composites. Mater Des 46:391–410

Martin RT, Bailey SW, Ebert DD, Fanning DS, Guggenheim S, Kodama H, Srodón Pevear DR, Wicks FJ (1991) Report of the clay minerals society nomenclature committee: revised classification of clay minerals. Clays Clay Miner 39:333–335

Massaro M, Collletti CG, Lazzara G, Riela S (2018) The use of some clay minerals as natural resources for drug carrier applications. J Funct Biomater 9:58. https://doi.org/10.3390/jfb9010058

Merriman RJ (2005) Clay minerals and sedimentary basin history. Eur J Mineral 17:7–20. https://doi.org/10.1127/0935-1221/200570017-0007

Merriman RJ (2006) Clay minerals and sedimentary basin history. Macla 6, XXVI Reúnion SEM/XX Reúnion SEA, 25–26

Merriman RJ, Peacor DR (1998) Chapter 2: very low-grade metapelites: mineralogy, microfabrics and measuring reaction progress. In: Frey M, Robinson D (eds) Low-grade metamorphism. Blackwell Science, London

Meunier A (2005) Clays. Springer Berlin/Heidelberg/New York, 472 pp. ISBN 3-540-21667-7

Meunier A (2013) Identification and characterization with microscopic methods. In: Fiore S, Javier Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA educational series. Publication no. 1, pp 73–88

Milliken RE, Bish DL (2011) Clays beyond Earth. Clays Clay Miner 59(4):337–338. https://doi.org/10.1346/CCMN.2011.0590400

Millot G (1970) Geology of clays. Springer, Berlin, 429 pp

Mitchell D, Vincent A (1997) Exploration and appraisal of plastic sedimentary clays for the fine ceramics industry. Appl Clay Sci 11:311–327

Mishra G, Dasf B, Pandey S (2018) Layered double hydroxides: a brief review from fundamentals to applications as evolving biomaterials. Appl Clay Sci 153:172–186

Modabberi S, Namayandeh A, López-Galindo A, Viseras C, Setti M, Ranjbaran M (2015) Characterization of Iranian bentonites to be used as pharmaceutical materials. Appl Clay Sci 116–117:193–201

Moore DM, Reynolds RC (1997) X-ray diffraction and the identification and analysis of clay minerals. Oxford University Press, New York

Moreno-Maroto JM, Alonso-Azcárate J (2018) What is clay? A new definition of "clay" based on plasticity and its impact on the most widespread soil classification systems. Appl Clay Sci 161:57–63

Mukherjee S (2013) The science of clays: applications in industry, engineering, and environment. Springer, Heidelberg

Murray HH (2000) Traditional and new applications for kaolin, smectite, and palygorskite: a general overview. Appl Clay Sci 17:207–221

Murray HH (2006) Current industrial applications of clays. Clay Sci 12(Supplement 2):106–112

Murray HH (2007) Applied clay mineralogy: occurrences, processing and application of Kaolins, Bentonites, Palygorskite-Sepiolite, and common clays, Developments in clay science, vol 2. Elsevier, 180 pp

Murray HH et al. (1993) Kaolins, kaolins and kaolins. In: Murray HH, Bundy WM, Harvey CC (eds) Kaolin genesis and utilization. , Special Publication 1. Clay Mineralogical Society of America, pp 1–24

Nagasawa K, Moro H (1987) Mineralogical properties of halloysites of weathering origin. Chem Geol 60:145–149

Nagendrappa G (2011) Organic synthesis using clay and clay-supported catalysts. Appl Clay Sci 53:106–138

Nagy B, Bradley WF (1955) The structure scheme of sepiolite. Am Miner 40:885–892

Nazir MS, Kassim MHM, Mohapatra L, Gilani MA, Raza MR, Majeed K (2016) Characteristic properties of nanoclays and characterization of nanoparticulates and nanocomposites. In: Jawaid M et al (eds) Nanoclay reinforced polymer composites, Engineering materials. Springer, Singapore, pp 35–55. https://doi.org/10.1007/978981-10-1953-1-2

Nieto F, Arroyo X (2013) Identification and characterization with microscopic methods. In: Fiore S, Javier Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA educational series. Publication no. 1, pp 73–88

Novelli G (1996) Applicazion medicali e Igieniche delle bentoniti. Atti Conv. "Argille Curative", Veniale F. (editor), Gruppo Italiano AIPEA, Salice Terme (PV), Tipografia Trabella, Milano

Novelli G (1998) Applicazioni Cosmetiche e Medicaliu delle argille smectiche. Cosmet News 122:350–357

Novelli G (2000) Bentonite: a clay over the centuries. Incontri Scentifici, V Corso di Formazione "Metodi di Analisi di Materiali Argillosi". Gruppo Itaiano AIPEA, pp 263–304

Odom IE (1984) Smectite clay minerals: properties and uses. Philos Trans R Soc London A311:391–409

Oliveira KCBF, Meneguin AB, Bertolino LC, Filho EC, Leite JRSA, Eiras C (2018) Immobilization of biomolecules on natural clay minerals for medical applications. Int J Adv Med Biotechnol 1(1):31–40

Onal M, Sarikaya Y (2007) Preparation and characterization of acid activated bentonite powders. Powder Technol 172(1):14–18

Pagano T, Sérgio M, Glisenti L, Diano W, Grompone MA (2001) Use of pillared montmorillonites to eliminate chlorophyll from rice bran oil. Ingenieria Química, 11–19

Paquet H, Clauer N (1997) (eds) Soils and sediments: mineralogy and geochemistry. 369 pp, Springer

Parfitt RL (1990) Allophane in New Zealand: a review. Aust J Soil Res 28:343–360

Patel HA, Somani RS, Bajai HC, Jasra RV (2006) Nanoclays for polymer nanocomposites, paints, inks, greases, and cosmetic formulations, drug vehicle and waste water treatment. Bull Mater Sci 29:133–145

Pearson A (2002) The competent nurse? Int J Nursing Practice 8(5):233–234. https://doi.org/10.1046/j.1440-172x.2002.00381.x

Peiró PS, Tejero SS (2014) Utilización terapêutica de la arcilla. In: Peloteraia: Aplicaciones médicas e cosméticas de fangos termales. Fundación Bílbilis, Torres AH (coordinador), pp 279–288

Plançon A (2001) Order-disorder in clay minerals structures. Clay Miner 36:1–14

Plançon A (2013) Identification and characterization of mixed-layer clay minerals by means of XRD of oriented clay mounts. In: Fiore S, Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance. AIPEA educational series, Pub. no. 1, pp 35–52

Plançon A, Tchoubar C (1977a) Determination of structural defects in phyllosilicates by X-ray powder diffraction – I. principle of calculation of the diffraction phenomenon. Clays Clay Miner 25:430–435

Plançon A, Tchoubar C (1977b) Determination of structural defects in phyllosilicates by X-ray powder diffraction – II. Nature and proportion of defects in natural kaolinites. Clays Clay Miner 25:436–450

Ponto BS, Berg JC (1918) Clay particle charging in apolar media. Appl Clay Sci 161:76–81

Pozo M, Calvo JP (2013) Madrid basin: a natural lab for the formation and evolution of magnesium clays. In: Pozo M, Galán E (eds) Magnesium clays: characterization, origin and applications,. AIPEA educational series. Publication no. 2, pp 229–282. ISBN: 978-88-7522-093-6

Pozo M, Calvo JP (2018) An overview of authigenic magnesian clays. Minerals 8(11):520. https://doi.org/10.3390/min8110520

Pozo M, Galán E (eds) (2013) Magnesium clays: characterization, origin and applications. AIPEA educational series. Publication no. 2, 380 pp. ISBN: 978-88-7522-093-6

Preissinger A (1963) Sepiolite and related compounds: its stability and applications. In: Clays and clay minerals. Proceedings of the national conference, vol 10. Pergamon Press, New York, pp 365–371

Price R, Gaber B, Lvov YM (2001) In vitro release characteristics of tetracycline HCl, khellin and nicotinamide adenine dineculeotide from halloysite: a cylindrical mineral. J Microencap 18:713

Pruett RJ, Pickering SM Jr (2006) Clays: Kaolin. In: Kogel E et al (eds) Industrial minerals and rocks, 7th edn. Society of Mining Engineers, Littleton, pp 383–399

Psyrillos A, Howe JH, Manningm DAC, Burley SD (1999) Geological controls on kaolin particle shape and consequences for mineral processing. Clay Miner 34:193–208

Putzoulu F, Papa AP, Mondillo N, Boni M, Balassone G, Mormone A (2018) Geochemical characterization of bauxite deposits from the Abruzzi Mining District (Italy). Minerals 8:298

Quantin P, Gautheyrou J, Lorenzoni P (1988) Halloysite formation through *in situ* weathering of volcanic glass from trachytic pumices, Vico's Volcano, Italy. Clay Miner 23:423–437

Rautureau M, Tchoubar C (1976) Structural analysis of sepiolite by selected area electron diffraction: relations with physico-chemical properties. Clays Clay Miner 24:43–49

Rautureau M, Tchoubar C, Mering J (1972) Analyse structural de la sepiolite par microdiffraction eléctronique. C.R Acad Sci 274:269–271

Rautureau M, Liewig N, Gomes CSF, Katouzian-Safadi M (2010) Argiles et Santé: Propriétés et Thérapies. Editions Médicales Internationales, Lavoisier, 184 pp. ISBN: 978-2-7430-1202-1

Rautureau M, Gomes CSF, Liewig N, Katouzian-Safadi M (2017) Clays and health: properties and therapeutic uses. Springer, Cham. ISBN: 978-3-319-42883-3

Reinbacher R (1999) Brief history of clay in medicine. Clay Miner Soc News 11:22–23

Reinbacher R (2003) Healing Earths: the third leg of medicine. 1st Books Library, Bloomington, 244 pp

Revuri V, Lee Y-K (2019) 2D material-based hybrid nanostructure for diagnosis and therapy. In: Biomedical application of graphene and 2D nanomaterials.

Rieder M, Cavazzini G, D'yakonov YS, Frank-Kamenetski VA, Gottardi G, Guggenheim S, Koval PV, Muller G, Neiva AMR, Radoslovich EW, Robert JL, Sassi FP, Takeda H, Weiis Z, Wones DR (1998) Nomenclature of the micas. Clays Clay Miner 46:586–595

Robertson RHS (1960) Mineral use guide. Cleaver- Hume Press, London

Robertson RHS (1986) Fuller's Earth: a history. Volturna Press, Kent, 421 pp

Robertson RHS (1996) Cadavers, choleras and clays. Bull Mineral Soc 113:3–7

Ross CS, Shannon EV (1926) Minerals of bentonite and related clays and their physical properties. Am Ceram Soc J 9:77–96

Ruiz-Hitsky E, Darder M, Alcântara ACS, Wicklein B, Aranda AP (2015) Recent advances on fibrous clay-based nanocomposites. Adv Polym Sci 267:39–86

Ruiz-Hitzky E, Darder M, Fernandes FM, Wicklein B, Alcântara ACS, Aranda AP (2013a) Fibrous clay-based nanocomposites. Prog Polym Sci 38:1392–1414

Ruiz-Hitzky E, Aranda P, Darder M, Fernandes FM (2013b) Fibrous clay mineral-polymer nanocomposites. Developments in clay science, vol 5, pp 721–741

Ruiz-Hitzky E, Darder M, Alcântara ACS, Wicklein B, Aranda AP (2017) Chapter 1: functional nanocomposites based on fibrous clays. RSC smart materials n° 22, pp 1–53

Santarén J (2013) Properties and applications of magnesium clays. In: Pozo M, Galán E (eds) Magnesium clays: characterization, origin and applications. AIPEA educational series, vol 2, p 331

Savechenkov TV (1862) Definition, Verlag Russe-Kaiser, Gessellschaft Mineralogy, St. Petersburg, URSS, p 102

Savic I, Stojiljkovic S, Savic I, Gajic D (2014) Chapter 15: Industrial application of clays and clay minerals. In: Wesley LR (ed) Clays and clay minerals: geological origin, mechanical properties and industrial applications. Nova Science Publishers, New York

Schoonheydt RA (2016) Reflections on the material science of clay minerals. Appl Clay Sci 131:107–112

Schroeder PA, Erickson GG (2014) Kaolin: from ancient porcelains to nanocomposites. Elements 10(3):177–182

Scott PW (1990) Brightness and colour measurement CEC/ASEAN training course on assessment procedures for clays and ceramic raw materials

Selinus O, Alloway B, Centeno J, Finkelman R, Fuge R, Lindh, U, Smedley P. (eds) (2005) Essentials of medical geology: impacts of the natural environment on public health. Academic Press/Elsevier, 812 pp

Shahidi S, Ghoranneviss M (2014) Effect of plasma pretreatment followed by nanoclay loading flame retardant properties of cotton fabric. J Fusion Energ 33:88–95

Shutava TG, Fakhrullin RF, Lvov YM (2014) Spherical and tubular nanocarriers for sustained drug release. Curr Opin Pharmacol 18:141–148

Silva JS, Vilarinho A, Barud HD, da Silva EC, Nunes LCC (2016) Fibrous and tubular clays to modified release of drugs: a review. Revista Matéria 21:204–212

Sokolova GV, Drits V (1971) Structure of palygorskite. Sov Phys Crystall 16:183–185

Srodon J (2013) Evolution of mixed-layer clay minerals in prograde alteration systems. In: Fiore S, Cuadros J, Huertas FJ (eds) Interstratified clay minerals: origin, characterization and geochemical significance AIPEA educational series, Pub. No. 1, p 41

Suárez M, Garcia-Romero E (2006) Macroscopic palygorskite from Lisbon volcanic complex. Eur J Mineral 18:119–126

Sudo T, Yotsumoto M (1977) The formation of halloysite tubes from spheritic halloysite. Clay Clay Miner 25:155–159

Suresh R, Borkar S, Sawant V, Shende V, Dimble S (2010) Nanoclay drug delivery system. Int J Pharm Sci Nanothecnol 3:901–905

Tang Q, Wang F, Tang M, Liang J, Ren C (2012) Study on pore distribution and formation rule of sepiolite mineral nanomaterials. J Nanomater 2012:382603

Tateo F, Summa V (2007) Element mobility in clays for healing use. Appl Clay Sci 36:64–76

Tateo F, Summa V, Gianossi ML, Ferraro G (2006) Healing clays: Mineralogical and geochemical constraints on the preparation of clay-water suspension (“argillic water”). Appl Clay Sci 33:181–194

Tateo F, Ravaglioli A, Andreoli C, Bonina F, Coiro V, Degetto S, Giaretta A, Menconi Orsini A, Puglia C, Summa V (2009) The in vitro percutaneous migration of chemical elements from a thermal mud for healing use. Appl Clay Sci 44:83–94

Thompson CJS (1914) Terra Sigillata, a famous medicament of ancient times. In: Proceedings of the 17th international congress of medicine vol 23, pp 433–434

Thorez J (1975) Phyllosilicates and clay minerals: A laboratory handbook for their X-ray diffraction analysis. Editions G. Lellote. Dison, Belgium, 579 pp

Thorez J (1976) Practical identification of clay minerals: a handbook for teachers and students in clay mineralogy. Editions G. Lelotte. Dison, Belgium, 90 pp

Thorez J (2003) L’argile, mineral pluriel. Bulletin de la Socité Royale des Sciences de Liège 72(1):19–70

Tosca N (2013) Geochemical Pathways to Mg-silicate Formation. In: Pozo M, Galán E (eds) Magnesium clays: characterization, origin and applications, AIPEA educational series, vol 2, pp 283–330

Uddin MK (2017) A review on the adsorption of heavy metals by clay minerals, with special focus on the past decade. Chem Eng J 308:438–462

Valeton I (1983) Paleoenvironment of lateritic bauxites with vertical and lateral differentiation. Geological Society, London, Special Publication 11 – residual deposits: surface related weathering processes and materials, 77–90 pp

Van Olphen H (1963) An introduction to clay colloid chemistry. Wiley Interscience Publishers, New York

Vaniman DT, Bristow TF, Bish DL, Ming DW, Blake DF, Morris RV, Rampe EB, Chipera SJ, Treiman AH, Morrison SM, Achilles CN, Downs RT, Farmer JD, Crisp JA, Morookian JM, Des Marais DJ, Grotzinger JP, Sarrazin P, Yen AS (2014) The first X-Ray diffraction analyses of clay minerals on Mars. 51st annual meeting of CMS. Everything is big: from nanoparticles to planets, Abstract Book 227-228

Vasilakos SP, Tarantili PA (2012) “In Vitro” drug-release studies from organoclay/poly (dimethyl siloxane) nanocomposite matrices. J Biomed Mater Res Part B 100B:1899–1910

Velde B (1992) Introduction to clay minerals. Chapman & Hall, London

Veniale F (1996) Argille Curative: Antefatti, Fatti e Misfatti. Atti Convegno “Argille curative”. Salice Terme (PV, Italy), 26–28 October, 1–11

Veniale F (1998) Applicazioni e utilizzazioni medico-sanitarie di materiali argillosi (naturali e modificati). Corso di Specializzazione, Gruppo Italiano AIPEA, 1–40

Veniale F (1999) Simposio “Argille per fanghi peloidi termali e per trattamenti dermatologici e cosmetici”. Montecatini Terme, May 14–15. Gruppo Italiano AIPEA, Pisa, Italy

Veniale F, Barberis E, Carcangiu G, Morandi N, Setti M, Tamanini M, Tessier D (2004) Formulation of muds for pelotherapy: effects of “maturation” by different mineral waters. Appl Clay Sci 25:135–148

Veniale F, Bettero A, Jobstraibizer PG, Setti M (2007) Thermal muds: prespectives of innovation. Appl Clay Sci 36:141–147

Viseras C, López-Galindo A (1999) Pharmaceutical applications of some Spanish clays (sepiolite, palygorskite, bentonite): some pre-formulation studies. Appl Clay Sci 14:69–82

Viseras C, Cultrone G, Cerezo P, Aguzzi P, Baschini MT, Valles J, López-Galindo A (2006) Characterization of northern Patagonian bentonite for pharmaceutical uses. Appl Clay Sci 31:272–281

Viseras C, Aguzzi C, Cerezo P, Lopez-Galindo A (2007) Uses of clay minerals in semisolid health care and therapeutic products. Appl Clay Sci 36:37–50

Viseras C, Cerezo P, Sanchez R (2010) Current challenges in clay minerals for drug delivery. Appl Clay Sci 48(3):291–295

Wagner U, Gebhard R, Grosse G, Hutzelmann T, Murad E, Riederer J, Shimada I, Wagner FE (1998) Clay: an important raw material for prehistoric man. Hyperfine Interact 117:323–335

Wang Q, O'Hare D (2012) Recent advances in the synthesis and application of Layered Double Hydroxides (LDH) Nanosheets. Chem Rev 112:4124–4155

Wang A, Wang W (2019) Nanomaterials from clay minerals: a new approach to green functional materials (Micro and Nano Technologies). Publisher Elsevier,1st edition, 693 pp, ISBN-13 :978-0128145333; ISBN-10: 0128145331

Wei W, Minullina R, Abdullayev E, Fakhrullin R, Mills D, Lvov Y (2014) Enhanced efficiency of antiseptics with sustained release from clay nanotubes. RSC Adv 4:488–494

Weiss A, Range KJ (1970) Superiority of hydrazine over potassium acetate in the formation of kaolinite intercalation complexes. In: Heller-Kalai L (eds) Proceedings of the international clay conference, Tokyo 1969, vol 2. Israel University Press, Jerusalem, pp 185–186

Wesley LR (2014) Clays and clay minerals: geologic origin, mechanical properties and industrial applications, Earth sciences in the 21st century. Nova Science Publishers, New York

Williams LB, Hillier S (2014) Kaolins and health: From first grade to first aid. Elements 10:207–211

Williams LB, Holland M, Eberl DD, Brunet T, Brunet de Courssou L (2004) Killer Clays ! Natural antibacterial clay minerals. Mineral Soc Bull 139:3–8

Wilson MJ (ed) (1987) A handbook of determinative methods in clay mineralogy. Blackie, London

Wilson MJ (2003) Clay mineralogical and related characteristics of geophagic materials. J Chem Ecol 29:1525–1547

Wilson MJ (2013) Rock forming minerals: sheet silicates, clay minerals, 2nd edn. Geological Society of London, London

Wilson I, Keeling J (2016) Global occurrence, geology and characteristics of tubular halloysite deposits. Clay Miner 51:309–324

Worrall WE (1975) Clays and ceramic raw materials. Applied Science Publishers, London, 203 pp

Worrall WE (1982) Ceramic raw materials. Pergamon Press, Oxford, 111 pp

Wu CN, Yang Q, Takeuchi M, Saito T, Isogai A (2014) Highly tough and transparent layered composites of nanocellulose and synthetic silicate. Nanoscale 6:392–399. https://doi.org/10.15376/biores.10.46310-6313

Yuen JWM, Chung TWK, Loke AY (2015) Methicillin-resistant *Staphylococcus aureus* (MRSA) contamination in bedside surfaces of a hospital ward and the potential effectiveness of enhanced disinfection with an antimicrobial polymer surfactant. Int Environ Res Public Health 12:3026–3041

Zhang D, Zhou C, Lin C, Tong D, Yu W (2010) The synthesis of clay minerals. Appl Clay Sci 50(1):1–11

Zhou CH, Keeling J (2013) Fundamental and applied research on clay minerals: From climate and environment to nanotechnology. Applied Clay Science 74:3–9

Zhou CH, Du ZX, Li XN, Lu CS, Ge ZH (2005) Structure development of hectorite in hydrothermal crystallization synthesis process. Chin. J. Inorg. Chem. 21(9):1327–1332

Zhou CH, Zhao LZ, Wang AQ, Chen TH, He HP (2016) Current fundamental and applied research into clay minerals in China. Applied Clay Science 119:3–7

Zhou CH, Tong D, Yu W (2019) Chapter 7: Smectite nanomaterials: preparation, properties and functional applications. In: Wang A, Wang W (eds) Nanomaterials from clay minerals: a new approach to green functional materials. Elsevier, 335–364 pp

Chapter 7
Interactions of Clay and Clay Minerals with the Human Health

Celso S. F. Gomes, Michel Rautureau, Jorge H. C. Gomes, and Eduardo A. F. Silva

Abstract This chapter is initiated with the record and discussion of the diverse uses of healing clay, both for internal applications involving geophagy and edible clay and for external or topical applications involving the practices called mud therapy and pelotherapy. The etiology and health consequence (benefits, risks, and mechanisms of action) of edible clay are discussed. Distinction is made between geophagy and pica. Distinction is made too between mud and peloid materials, characterized in terms of diversity and typology. One type of peloid, the *designed and engineered peloid*, is enhanced, since its simple composition, manipulation, and modification allow a better understanding of its medical or cosmetic performance. Peloid's function, benefits, risks, and mechanisms of action and edible clay mechanisms of action are reported and discussed. Databases of publications on medical and cosmetic pelotherapy are reported. The role of clay minerals in biocomposites, and in controlled drug delivery systems for pharmaceutical and medical applications, the case of halloysite nanotubes, is discussed. The bactericidal activity of some minerals is reported and explained. The chapter ends identifying and discussing diseases whose etiology is attributed to clay such as podoconiosis, Mseleni joint's disease, Kashin-Beck's disease, and Keshan's disease, as well as other adverse effects caused by clay and clay minerals.

C. S. F. Gomes (✉) · J. H. C. Gomes · E. A. F. Silva
Department of Geosciences, Researcher of the Research Unit "GeoBioTec",
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

M. Rautureau
Docteur d'État ès Sciences Physiques, Retired of University of Orléans, Orléans, France

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_7

7.1 Typologies of Curative or Healing Clay

Kaolinitic clay, smectitic clay, and palygorskite-sepiolite clay are the three types of curative or healing clay and of edible clay more utilized for both therapeutic and cosmetic purposes.

Kaolin and bentonite are both geologic and commercial names attributed to particular types of *kaolinitic clay* and *smectitic clay*. The name *fibrous clays* encompasses both *palygorskite*- and *sepiolite*-bearing clays. Kaolin is a clay essentially constituted by clay minerals belonging to the kaolinite group, and is considered an effective homeostatic for wound cure, defined homeostasie as the tendency for the electrostatic equilibrium of body liquids. Also, there are evidences that several varieties of *kaolin* have antibacterial properties, and others have been utilized too in the controlled delivery of drugs. *Kaolinite*, whose individual crystals exhibit platy shapes, regular or irregular, and *halloysite*, whose individual crystals show either platy, or tubular, or yet spherical morphologies, are the main clay mineral species that could be present in kaolin. Compared to platy *kaolinite* forms, *halloysite* tubular forms have higher specific surface areas and consequently greater potential to bind, in particular, cationic drugs, enabling the conditioning and control of their release rate, good in medical applications.

Bentonite is an *especial clay* essentially constituted by clay minerals belonging to the *smectite group*. *Smectite minerals* which are characterized by much higher specific surface areas and unit layer charges compared to *kaolinite minerals* have interlayer-free and size-variable spaces where drug molecules could be entrapped or encapsulated enabling its biomedical use as drug delivery systems.

Within the clay mineral species constituting the *smectite group*, *montmorillonite* are the most used species in pharmaceutical formulations and in healing applications. Within the group of fibrous clay minerals, *palygorskite* and *sepiolite* are species with pharmaceutical interest for curative applications.

Clay – and the quasi-amorphous or amorphous inorganic materials and the organic materials, both currently associated with it – constitutes good support and vehicle for fixation, growth, and transportation of organic colloids and microorganisms (bacteria and fungi, some eventually pathogenic) and for fixation of chemical elements (some potentially toxic) naturally existing or that could be introduced into the occurrence environment, reason why the sanitary safety control both chemical and microbiological of *healing clay* (both *edible clay* and *healing mud/peloid*) should be a prerequisite before its use.

7.2 Healing Clay for Internal Uses: Geophagy and Edible Clay

Substantial part of this topic had been reported and discussed in the article entitled “Healing and edible clays: A review of basic concepts, benefits and risks” that recently was published by Gomes 2018 in the scientific journal *Environmental Geochemistry and Health*, although somehow modified and updated.

In the case of human health, man through time, initially and still today in certain regions and places of the world, through the so-called Empirical Medicine, was verifying that certain minerals had positive effects on his health. This is the case of *geophagy* or *geophagia* defined as the deliberate and uncontrollable urge to eat earth, usually clayey soil and clay, by man and other animals or to eat medicinal preparations in which these minerals participate, being still common practice in traditional rural societies, assuming that it is a response subconscious for toxic diets.

Geophagy is still common in some communities in certain countries, particularly of Africa (particularly in Nigeria, Tanzania, Ghana, Kenya, Uganda, and South Africa), South America, and Asia (particularly in India and Bangladesh), for therapeutic and religious purposes or even to kill hunger. Geophagy was first reported by Aristotle and is a current practice in mammals, birds, and reptiles. In the case of man, geophagy, an ancient practice that has already been much generalized, still takes place in some regions of the world (Wilson 2003).

Geophagy was further described by Dioscorides and Avicenna in 40 B.C. and 1000 A.C., respectively (Halstead 1968). von Humboldt wrote in his travel reports from South America between 1799 and 1804 that clay was eaten to some extent at all times by the Otomac tribe along the Orinoco River, and in Peru, he saw mothers give their children lumps of clay to keep them quiet (*In*: Halstead 1968).

According to Abrahams 2005, 60–90% of children (5–14 years) of Kenya practice geophagy consuming, on average, 20 g/day of soil.

Geophagy is justified in many cultures by therapeutic, nutritional, and/or religious reasons, goes back to prehistoric times, and is widespread across the world; clayey soil or clay ingestion is an ancestral practice still current in several regions of all continents, reflecting cultural practice, religious belief, and physiological needs (nutritional or therapeutic).

On the geophagy subject, the reading of the following papers is recommended: Reilly and Henry 2000; Woywodt and Kiss 2002; Wilson 2003; Hooda et al. 2004; Abrahams 2005, 2010, 2012; Figueiredo et al. 2010; Young 2011; Njiru et al. 2011; Abrahams et al. 2013; Henry and Cring 2013; and Lambert et al. 2013; Huebl et al. 2016; Gundacker et al. 2017; and Kambunga et al. 2019.

Soil or clay ingestion known as geophagy is a behavior commonly observed among peoples on all continents (Humboldt 1985; Laufer 1930; Hunter 1973; Vermeer and Frate 1979; Hunter and De Kleime 1984; Johns 1986; Johns and Duquette 1991; Reid 1992; Abrahams and Parsons 1996; Aufreiter et al. 1997; Geissler et al. 1997, 1998, 1999; Grigsby et al. 1999; Mahaney et al. 2000; Tateo et al. 2001; Saathoff et al. 2002; Browman 2004; Nchito et al. 2004; Londoño 2007; Ghorbani 2008; and Figueiredo et al. 2010).

Regarding South America, the German biogeographer, naturalist, and explorer von Humboldt (1769–1859), in his travel reports from South America between 1799 and 1804 (In: seven-volume “Personal narrative of travels to the equinoctial regions of the new continent, during the years 1799–1804”), recorded the Otomacs’ habit of eating significant quantities of clay extracted from the alluvial beds from the Orinoco River, during high water levels, a period where the food seemed to be scarce, although geophagy was practiced all year long. And von Humboldt in Peru saw mothers give their children lumps of clay to keep them quiet. Otomacs enjoyed eating clay, they cooked it and made small balls to be carried and consumed as a snack or as a small meal, and they also had recipes such as "clay bread," the result of mixing clay with corn and turtle or caiman fat, only eaten after undergoing fermentation (Gumilla cited in Rosenblat 1964; Halsted 1968).

Browman 2004 reports 24 types of earths used by the inhabitants of Central Andes, in Bolivia and Argentine, either as a food supplement or as drugs. Samples of those earths have shown to be composed of phyllosilicates, sodic and calcium earths, sulfur minerals, and another group made up of iron and copper salts. The author reports the traditional names "Pása" and "Chágo" for raw materials composed of mixed clay minerals (*smectite*, *kaolinite*, *chlorite*, *illite*), being highly appreciated earths for their properties to alleviate gastrointestinal upsets related to phytotoxins present in domesticated plants, such as *solanine* in potatoes or *saponin* in quinoa. Also, Rowe 1946 stated that in the Inca Empire "A quantity of edible clay was collected and exchanged with some frequency in the southern mountains."

London 2007 reports, in the northwest Amazon basin, in Colombia, the ingestion of clay minerals in solution by the Uitotos indigenous society as a therapy for alleviating digestive upsets, detoxification of the liver, and counteracting poisonous compounds. The raw materials were dominated by clay, and the composition was the same as that reported by Johns and Browman.

According to Ferrell 2008, the direct consumption of the so-called edible earths for medicinal and spiritual purposes occurs worldwide and is deeply rooted in the so-called folk medicine and religion. The religion factor is well represented in Chimayo, New Mexico, where close to the Sanctuary clay is extracted from a pit and ingested, for spiritual healing, by the peregrines.

Although the incidence of geophagy is decreasing in the world, the practice remains common in many cultures with a significant proportion of women (65.3%) engaging in geophagy before pregnancy and 46.7% during the second gestational trimester (Saunders et al. 2009; Shinondo and Mwikuma 2009).

In most African cultures, geophagy is culturally accepted especially among children and pregnant women. In Africa there are countries, where GiP (geophagy in pregnancy) prevalence of up to 84% has been observed in Uganda, and of up 75% in Kenya where 70% of school children are geophagous, and in Nigeria, the most populous country in Africa, the GiP prevalence is estimated at 50% (Njiru et al. 2011). Also, according to Sheppard 1998, and Geissler et al. 1999, the practitioners of *geophagy* can consume about 30–50 g/day, and more women (particularly during pregnancy believed to help in relieving nausea and emesis and during lactation) than men are engaged in geophagic practice.

Geophagy is often associated with the eating disorder called *pica* that could be hazardous because the individual addicted to earth substances does not distinguish the safe ones from the hazardous ones that can contain toxic chemical elements or compounds and/or pathogenic microorganisms (bacteria and fungi).

Pica is defined as the purposive consumption of substances that the consumer does not identify as food. For Danford 1982, *pica* encompasses *geophagy* (earth eating), *amylophagy* (raw starches eating), and *pagophagy* (ice eating). Several etiologies of *pica* have been proposed, including hunger, micronutrient deficiencies, gastrointestinal distress, and increased exposure or susceptibility to pathogens (Young et al. 2008).

Pica is an unusual form of carving, just like as craving for chocolate or as a type of "reward"; soil eating has an addictive behavior. The reasons behind *pica* could be quite different and also quite multilayered.

Geophagy practice remains relatively mysterious. Henry and Cring 2013, on a text entitled "Geophagy: An Anthropological Perspective", state that:

> *Although the practice of geophagy being documented worldwide for at least two millennia and studied for several centuries the reasons why humans consume soil are still a matter of puzzlement for many and a subject of research for some. Indeed, researchers from fields as diverse as chemistry, and geography, medicine and geology, sociology and paediatrics, history of religion and pedology, nutrition and primatology have investigated the practice, the practitioners, and the product consumed.*

Henry and Cring 2013 disclose interesting information on anthropological, cultural, archeological, and biological aspects of geophagy, as well as the current and future state of geophagy.

Not only soil, particularly clayey soil, and clay are consumed in geophagy. Clay-based materials that had undergone low-temperature firing modification, as is the case of red ware ceramics of pottery typology, more precisely of terracotta, have been consumed too as a common practice in the Iberian countries, Spain and Portugal, from Middle Ages to Early Modern Age. The terms *bucarophagy* and *pucarophagy* are related to the terms "búcaros" and "púcaros" attributed in Spain and Portugal, respectively, to small ceramic containers (with capacity as a rule not higher than 1 l) renowned for cooling and scenting drinking water, the cooling due to the high porosity of the ceramic containers promoting water evaporation, the scenting due to natural scent or to the addition of ground aromatic herbs to the slip. Broken small pieces of "búcaros" and "púcaros" were eaten by Spanish and Portuguese early modern women, after having drunk the water contained in them. This custom, called *bucarophagy* and *pucarophagy*, was widely widespread among the nobility particularly in fifteenth, sixteenth and seventeenth centuries, and its origin would date back to the ninth century, quite possibly following Arabic conquest (Seseña 1991), and most probably the Arabs having acquired the custom from the Persas. The custom of eating "púcaros" and "búcaros" was maintained up to nineteenth century. Bucarophagy and pucarophagy reached high popularity in the Iberian Peninsula that starting in the seventeenth century similar ceramic containers or vases which were produced various Spanish American Domains in the so-called Eastern Indias had been exported to Southern European countries, particularly to Spain and Italy. Tonalá, near Guadalajara, Mexico, was one important producing centre. Specimens of "búcaros de Indias" and of "búcaros" and "púcaros" produced in Spain and Portugal can be seen in various museums, such as Museo Civico

Medievale, in Bologna, Italy, and Museo de América, in Madrid, Spain. The "búcaros de Indias" are distinguished from those produced in the Iberian Península by its surface finishing, burnished using rolled stones, and as rule, by black colour. Lorenzo Legati, a physician and teacher at the University of Bologne, in his book 3, chapter XXII, "De' Vasidelle Terre Medicinali" of the Museo Cospiano (1677) reports important details of bucarophagy. Also, Lorenzo Magalotti (1825) describes the use of "bucaros de Indias" in the eight letters he addressed to Marquise Ottavia Strozzi, a noblewoman who owned a collection of around 300 pieces.

The book written by the French countess Marie-Catherine d'Aulnoy in 1691 – "Relation du Voyage d'Espagne" (Valenzuela 1967) describes well the custom of eating "búcaros" she had observed in a voyage she made to Spain in 1679, stating that "women have a great passion for these ceramic containers, which usually causes them obstructions, the stomach and the belly inflate and become hard as stone, and they are as yellow as quinces." Théophile Gautier (1845) in his book "Voyage en Espagne" recorded with disgust the practice of bucarophagy in Madrid.

The Portuguese "púcaros" have preceded the Spanish "bucaros," and as a rule they display a poorly burnished red surface, with or without decoration, a common characteristic of all these small ceramic containers which actually can be found in some museums. One "búcaro" has been represented by Diego Velázquez in its well-known painting "Las Meninas."

Studies carried out in clayey samples and "púcaros" and "búcaros" fragments from well-identified sources, in Portugal (Estremoz, Montemor o Novo, and Lisboa) and Spain (Salvatierra de los Barros, in Badajoz, and Talavera), where "púcaros" and "búcaros" had been fabricated, confirm that iron oxide (hematite) and hydroxide (goethite) are present in the raw materials, and that the clay minerals montmorillonite, illite and kaolinite are, as a rule, present too. The clayey material from Estremoz is a red residual soil (terra rossa) with origin from local marble weathering, and the clayey material from Lisbon is a residual soil from local basalt weathering. The "púcaros" of Estremoz commonly include in the ceramic paste little fragments of marble which favour porosity. The high iron content (could be higher than 10% expressed as Fe_2O_3) and the relatively high calcium and magnesium contents found in "púcaros" and "búcaros" could justify the medicinal interest for chewing their fragments. Within the references found in the literature about this interesting subject, some deserve to be mentioned: Michaelis Vasconcellos 1905; Seseña 1991, 2009; Valenzuela 1967; Franquelo et al. 2001; Rovira and Gaitán 2010; Newstead and Casimiro 2018; Domenici 2019; Garcia Rodriguez and Àlvarez Garcia 2019.

The prevalence of geophagy among pregnant women in Africa has been reported to range from 28% to 100% (Izugbara 2003; and Geissler et al. 1998).

Young 2010, 2011, and Young et al. 2010a, b, had carried out an interesting investigation about *pica* etiologies among a significant population of 2368 pregnant women on Pemba Island, Zanzibar, Tanzania, and they found that the prevalence of geophagy on Pemba Island was markedly lower (5.2%) and that the amount of earth (kaolin-bearing clay soil) consumed was 26.5 g/day. In Kenya, where clay is selectively identified and sold in markets, the consumption within pregnant women is 65% of clay that is collected from termite mounds rich in clay minerals and which is eaten at an average of 30 g/day. The last authors referred to, although proposing further research, did find out that geophagy was strongly positively associated with iron deficiency, anemia, and some gastrointestinal morbidities.

On the one hand, clay due to its characteristic high cation exchange capacity may reduce micronutrient cation absorption by consumers, as could be the case of Fe^{2+}. On the other hand, clay could have a protection action, adsorbing viruses, bacteria, and chemical poisons.

In other studies, the amount of consumed soil is reported to be between 5 g and 219 g, and the frequency ranges from one to twenty times per day (Geissler et al. 1999; and Abrahams 1997).

Pica is common within women, mainly of Asian and African pregnant women, who have a strong desire to eat soil and calabash chalk, i.e., non-food and non-nutritive substances (Al-Rmalli et al. 2010).

According to Welsh et al., there are three theories to explain the eating of calabash chalk:

1. Taste and mental satisfaction.
2. Anemia and malnutrition.
3. Protective action of the stomach.

Mishra and Roy 2015 revealed that clay eating is historically associated with treatment for cholera and bacterial infections and point out the importance to understand the clinic relevance of specific types of clay across the world, including India, Ethiopia, and other African countries.

Kutalek et al. 2010, and Ozumba and Ozumba 2002, report microbial contamination caused by the habit of eating clay soil, especially among pregnant women, is still a common practice in many countries, particularly in Africa, such as Tanzania, Nigeria, Guinea, Senegal, Cape Verde, Ivory Coast, Zambia, Ghana, Kenya, Swaziland, and South Africa; in America, such as Haiti, Peru, Panama, Guatemala, Mexico, and the USA (in southern rural areas); in Asia, such as Indonesia, India, and China; and in Oceania.

The etiology and health consequences of geophagy are still poorly understood. Various hypotheses exist, and there are conflicting studies to whether soil consumption may be either beneficial alleviating gastrointestinal upset like nausea and heartburn, antidiarrheal, detoxifying food, source for micronutrients and for iron deficiency, or deleterious, source of toxic metals and toxins.

Geophagy can be both beneficial and detrimental. Its health effects depend on the amount and composition of the ingested soils, which is subjective to the geology and soil formation processes. In most cases, the negative health effects concomitant with the practice of geophagy eclipse the positive effects. Therefore, knowledge about the nature of geophagic material and the health effects that might arise from their consumption is important. The type of consumed soil, individual motives, and consumption habits and the clinical aspects deserve more research. Soil sources could be diverse: riverbanks, swamps, red and white termite mounds, sun-dried bricks, and clay lumps bought in open local markets.

The practice of geophagy has been associated with health or developmental problems: iron (Fe) deficiency (Danford 1982), mechanical bowel disorder (Key Jr et al. 1982), and nutrition dwarfism (Prasad et al. 1961).

The reasons for soil/clay intake do not yet have scientific support, despite the significant number of researchers who have studied this popular practice: Woywodt and Kiss 2002; Izugbara 2003; Hooda et al. 2004; Kikouama et al. 2009; Brand et al. 2010; Abrahams 2010; Davies 2010; and Ekosse and Jumbam 2010.

Several hypotheses have been considered to explain geophagy, one of which is the need for a mineral nutrient supplement to compensate for dietary deficiencies. Soil/clay-based ingestion to treat certain internal organic affections can be explained on a scientific basis by the adsorbent and absorbing power of the clay and by the yielding to the organism of chemical elements (e.g., Fe, Na, and Ca) in it reversibly attached.

It is also demonstrated that many of the chemical elements present in the natural environment, more precisely in soil and drinking water, such as Si, Fe, Ca, Mg, Mn, I, Se, Cr, Cu, Mo, and Zn are bioessential.

In fact, health problems related to dietary deficiencies, deficiencies of certain chemical elements, for example, iodine (I), responsible for the disease called *goiter*, enlargement of the thyroid gland, and *cretinism*, mental retardation with physical deformations, are known, since they were common in some regions of Ancient China, Greece, and Egypt and treated empirically with marine algae (Selinus 2002). However, recent studies conducted at the Institute of Molecular Pathology and Immunology at the University of Porto (IPATIMUP) indicate that excess iodine is responsible for thyroid cancer. Also, it is recognized that soils and aerosols of the coastal and coastal zones are richer in iodine, compared to the soils and aerosols of continental zones.

Lifestyle, particularly the diet, is an important environmental factor that decisively conditions human health. There is an old aphorism “We are what we eat” that expresses the situation well. However, it is not enough to have access to food, also importing “Knowing how to eat,” that is, knowing how to select food in terms of quality and quantity, just to satisfy the correct functioning of the body throughout the various phases of life. In order to achieve this goal, the contribution of the so-called Nutrition Sciences is very important.

Effectively the discussion of such food cannot be limited to considerations of nutritional values, macronutrients and micronutrients, and the energy that foods provide. It is essential to make a balanced diet, avoiding foods already prepared and packaged, usually with excess fat, salt, and sugar.

In the 1980s of the twentieth century came the concept of functional food. Functional foods have been developed with the aim of promoting better health protection, reducing the risk of disease, and being able to integrate a normal diet. Thus, diets can integrate so-called probiotics (lactic acid bacteria and bifidobacteria that improve intestinal microflora, favor the immune system, and lower cholesterol), prebiotics (nondigestible oligosaccharides that promote the growth of intestinal bifidobacteria), phytochemicals (antioxidants such as vitamin C, carotenoids, thiols, and indoles), bioactive peptides, omega-3-type unsaturated fatty acids, mineral salts, and trace minerals or oligominerals.

Antioxidants are substances that are able to protect the body from the oxidation processes that occur constantly. Certain enzymes; vitamins such as A, C, and E; and minerals, such as zinc and selenium, are examples of antioxidants.

Oxygen being essential for life can also be a source of toxicity. Many of the harmful effects are attributed to free oxygen radicals, which are highly unstable and as such react rapidly with neighboring molecules initiating a process called oxidative stress causing damage. The body produces antioxidants that neutralize the effects of constantly formed free radicals as a natural consequence of metabolism. However, exposure at many risk factors, such as smoking, sedentary lifestyle, obesity, stress, etc., determines an exacerbated production of free radicals rendering the body's natural defenses insufficient. Therefore, this justifies the need to use mineral-vitamin antioxidant supplements.

For omega-3 fatty acids, this name was assigned to a family of polyunsaturated fatty acids. The primordial acid of the omega-3 family is alpha-linolenic acid (ALA), the short-chain fatty acid obtained through the diet, particularly when it comprises nuts, green leafy vegetables, and flax seeds and which is described as essential, although it is not as essential as vitamins and minerals. However, from the point of view of human nutrition, long-chain omega-3 fatty acids, *eicosapentaenoic acid* (EPA) and *docosahexaenoic acid* (DHA), which are particularly rich in seafood and fatty fish, are considered to be much more important, because these are the forms that the body requires.

In order to take care of and avoid the health risks that certain foods may constitute, many countries have agencies for food safety and quality. In Portugal, it was only at the end of 2005 that the Food and Economic Security Authority (ASAE) was created, which became the only public institution responsible for food safety and quality, previously attributed to three public institutions and, as such, unsatisfactorily satisfied due to uncoordinated and overlapping competencies.

Clay, a geomaterial of common occurrence on/or near the surface of the Earth, has been used by man since the Antiquity to satisfy basic utilitarian purposes (e.g., as a building material for his dwellings, used alone or in association with other natural materials) and for therapeutic and cosmetic purposes.

There are several types of clay, dependent on the lithology of the parent rock and the process that led to its formation due to the alteration, both meteoric and deuteric, of the primary minerals of the parent rock. Some of these types of clay have been used by man for therapeutic purposes, in the case of "healing clay"; for therapeutic and nutritional purposes, in the case of "edible clay"; or still for cosmetic purposes in the case of "cosmetic clay" and "mask clay."

The concept and function of "edible clay" is more limited than the concept and function of "curative clay." Effectively, the function of "edible clay" is limited to internal application through ingestion in the form of wafer or biscuit prepared with

Fig. 7.1 Woman from Haiti, in Port-au-Prince, where food is scarce and expensive, preparing one set of cookies made of clay, salt and animal fat, consumed in particular as dietetic supplements by pregnant women (*in* National Geographic, PT, November, 2008, nº 92, 88–91

clay/animal fat/drinking water mixture or as suspension prepared with clay/drinking water mixture (Fig. 7.1).

With regard to clay/human body interaction, clay particles could adsorb and make available for incorporation through ingestion, both bioessential and toxic elements (mostly *heavy metals*); also, they could adsorb and make available for elimination or excretion of any potential toxic elements or toxins which had been ingested or metabolically produced.

7.2.1 Benefits and Risks of Edible Clay

The name *edible clay* is applied to the clay that is deliberately ingested by humans as cookies or as clay/potable water dispersions; the clay can act as a source of mineral micronutrients and as a protective material against pathogens and toxins (detoxification of noxious or unpalatable compounds present in the diet); the clay can act too as an antacid for gastric acidity compensation and neutralization (Rautureau et al. 2017). Experience shows that the mineralogical and chemical compositions of "edible clays" are the conditioning factors of adsorbent and absorbent power and also the alkalinity of these clays, which justify the health benefits of their users.

Constipation as well as the reduction of the adsorption capacity of elements or compounds (e.g., in medicines when taken together with clay) may constitute a risk for the ingestion of edible clay or curative clay.

Functioning as drugs, the natural geophagic materials that correspond to *edible clays* should be chemically safe for consumers.

The EMA (European Medicines Agency), in 2008, for the oral exposure of pharmaceutical drugs, had established the upper limits for PDE (permitted daily exposure) relative to essential trace minerals such as Cr, Mo, Ni, V, Cu, Mn, Zn, and Fe. Regarding the heavy metals, the ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) Q3D had established, in 2013, the technical requirements (guidelines) for registration of pharmaceuticals for human use and, classified the most potentially toxic elements (heavy metals included) into three classes: *Class 1*, As, Cd, Hg, and Pb; *Class 2*, Co, Ni, Ag, Au, V, and Ir; and *Class 3*, Ba, Cr, Cu, Li, Mo, Sb, and Sn, based on their PDE and likelihood of occurrence in the drug products.

In general, the chemical composition of the geophagic materials described in the previous paragraph shows contents in those elements much higher than the ones established as upper limits. Naturally not all *edible clays* are equal, with some being more chemically and microbiologically safer than others. Also, whenever clay water dispersion or "argillic water" or "clay water" is ingested, the water quality is another important requisite, and it should be chemically and microbiologically safe.

WHO (2011) and EU (2011) established the guidelines or standards for quality of drinking water appraisal.

On the one hand, the internal use of *edible clay* is particularly reckoned as a potential means for:

1. Dietary supplementation of the mineral nutrients necessary for the synthesis of new tissues.
2. Combating iron deficiency or anemia.
3. Detoxification of noxious or unpalatable compounds present in the diet.
4. Relief of abdominal pains (heartburn) with accompanying vomiting.
5. Management of nausea and its associated emesis during the early stages of women pregnancy.

On the other hand, the ingestion of *edible clay* can cause health risks, such as constipation as well as reduction of the adsorption capacity of bioessential chemical elements, such as Fe, Zn, Mg, Ca, Se, etc., or of bioactive pharmaceutical compounds existing, for instance, in *drugs* if almost simultaneously taken with the *clay*. Also, some metals and metalloids, such as Pb, Hg, Cd, Cr, Sb, Ba, U, As, and Se, could be present in the *edible clay* in such concentrations that could make it toxic and poisonous, particularly due to their easy assimilation and bioaccumulation, i.e., the gradual buildup over time of a chemical element or compound in a living organism.

Toxicity much depends on for how long and frequent is the intake of *edible clay* and, naturally, of the nature of the chemical species (oxidation states) and bioavailability of the metals and metalloids referred to.

Davies et al. 2008; Brand et al. 2010; Ekosse and Jumbam 2010; and Jumbam 2013 discuss the possible effects on human health of the chemical composition, particularly of heavy metals, caused by geophagic materials.

Al-Rmaldi et al. 2010, report the health risk of geophagic practices by pregnant Bangladeshi women living both in Bangladesh and in the UK, since they are exposed to high concentrations of As, Pb, Cd, and Mn when they eat baked clay named Sikor, also purchased from shops in the UK, and in regard to As in Bangladesh, the As of the clay is accumulated with the As from contaminated drinking water. The authors also mention how important would be the evaluation of the bioavailability of As and other toxic elements as well as the clinical evaluation of the adverse effects.

Geophagy among pregnant women is common in many cultures. In some African countries, its prevalence of up to 84% has been observed. In Nigeria, the most populous country in Africa, the prevalence is estimated at 50%. The practice has been associated with religious practice, culture, and famine (Njiru et al. 2011). According to these authors, it is postulated that geophagy in pregnancy is due to micronutrient deficiencies, cultural influences, and gastrointestinal upsets. Despite their potential to supply micronutrients, soils interfere with bioavailability of micronutrients leading to micronutrient deficiency and can also act as a pathway for ingestion of geohelminths and heavy metals, putting woman and fetus at risk. The same authors consider that it is imperative to enquire whether pregnant women are geophagous and discourage geophagy, strengthen and expand the existing supplementation programs, and mandate flour fortification to enhance population-wide iron supply and safer pregnancies.

Recently Bonglaisin et al. 2011, discuss the potential hazardous effects of intake of Pb, Cd, and Hg related to kaolin-eating after analyzing geophagic kaolin samples from Cameroon and Nigeria sold in open markets and finding in them relatively high concentrations of those highly toxic heavy metals.

Samples of the famous *eko clay* were analyzed. Villagers outside of Uzalla, in Nigeria, mine blocks of kaolinitic clay from a depth of 30–90 cm from the surface and then sun-dry and smoke those blocks transforming them into a substance called *eko* that is sold in local markets. *Omumu clay* is an *edible clay* that is highly traded in open markets and consumed in Nigeria by pregnant women to manage nausea and emesis (vomiting) usually associated with the early stage of pregnancy, particularly during the first trimester. Both edible *eko* and *omumu* clays are baked earthen materials used to combat such discomfort.

As a matter of fact, geophagic clayey soil usually undergoes some preparation: air-dried, baked, smoked, salted, and mixed with herbs or water (Reilly and Henry 2000).

More recently yet Lar et al. 2014, and Owumi and Oyelere 2015, have chemically analyzed these geophagic clays since they are potential sources of heavy metals with health implications in women and children who consume them.

Gomes et al. 2009, in a study of *edible clays* sold in open and public markets and consumed in the islands of Cape Verde' archipelago besides high contents of Cr, Cu, Pb, Mo, Zn, V, U, and Th have identified too high contents of rare earth elements (for instance, Ce, 1356 ppm, and La, 562 ppm). Such clays particularly rich in the clay minerals smectite and illite are the weathering products of phonolite, alkaline extrusive volcanic rock with occurrences in the island of Boa Vista of the same Cape Verde archipelago.

Abrahams 2013 reports that the adsorption/absorption properties of certain edible clays when ingested can cause iron deficiency anemia, zinc deficiency, hypokalemia, and hyperkalemia. Also, ingestion of untreated clay or not sterilized clay can expose the consumer to parasites and to pathogenic bacteria and fungi.

Both benefits and risks of the use of *edible clay* are particularly well reported: Prasad et al. 1961; Key Jr et al. 1982; Danford 1982; Hunter and De Kleime 1984; Vermeer and Ferrell Jr 1985; Ziegler 1997; Aufreiter et al. 1997; Wiley and Katz 1998; Mahaney et al. 2000; Woywodt and Kiss 2002; Saathoff et al. 2002; Hooda et al. 2002, 2004; Kwong and Henry 2003; Izugbara 2003; Nchito et al. 2004; Tayie 2004; Trivedi et al. 2005; Abrahams et al. 2006; Tateo et al. 2006; Kikouama et al. 2009; Abrahams 2010; Al-Rmalli et al. 2010; Young 2010, 2011; Ekosse and Jumbam 2010; Kikouama and Baldé 2010; Njiru et al. 2011; Ekosse and Ngole 2012; Abrahams 2013; Mwalongo and Mohamed 2013; Lambert et al. 2013; Henry and Cring 2013; Nyanza et al. 2014; and Owumi and Oyelere 2015; and some of them being briefly shown hereunder.

According to Abrahams 2013, clayey soil and clay can be ingested as a food supplement during famine times; they can be ingested too for detoxification.

According to Young 2011, *edible clay* could provide a dietary supplement of the trace elements referred to as well as of other micronutrients. Also, according to Williams and Hillier 2014, an association between anemia and geophagy has been recognized since Roman times.

With regard to benefits, the authors emphasize a double effect: clay chemical composition enables the release of bioessential trace elements, such as iron, zinc, magnesium, and calcium, whereas clay mineralogical composition enables its use in the treatment of digestive diseases.

Williams and Hillier 2014 with regard to the risks enhance the following: contamination of pathogenic microorganisms, contamination of toxic elements, constipation, and reduction of absorption capacity of drugs.

Geo-helminthiasis caused by parasites that live in soil and clay is one of the most widespread parasites in the world, affecting almost 2000 million people all over the world (WHO, 2002).

Pathogenic agents, such as *Ascaris lumbricoides*, *Trichuris trichiura*, and *Uncinaria* sp., depend on many environmental variables during their early stages of life to become infectious for humans. Some of these variables include soil temperature, weather, air humidity, and soil properties. A first approach to assess this issue was attempted in 2005 with the study “Influence of geological factors on the prevalence of soil transmitted helminthes in Colombia” (Valencia et al. 2008). The main objective was to identify the most relevant environmental variables in an epidemiological sense.

Benefits

Gastroenterological diseases:

Diarrhea, colitis, nausea, colopathy, and ulcers.

Source of mineral nutrients:

Dietary supplementation, in case, for instance, of Fe, Zn, and Mg deficiencies.

Risks

Microbiological contamination:

Pathogenic microorganisms, both present in the natural geomaterial and acquired during its manipulation, baking being not a sufficient process for their inactivity.

Contamination of toxic trace elements:

Pb, Cd, Hg, Al, As, etc., through enteric incorporation.

Constipation and reduction of the gastrointestinal absorption capacity of drugs simultaneously taken with the edible clay.

The determination of both essential and toxic elements existing in the clayey soil commonly consumed by pregnant women, in order to assess safety, has been recently carried out, for example, in Tanzania by Mwalongo and Mohamed 2013 and Nyanza et al. 2014, and in Nigeria by Lar et al. 2014; Igeoma et al. 2014; and Owumi and Oyelere 2015.

Kikouama and Baldé 2010 to compensate eventual dietary deficiencies in Fe and Zn have designed clay-containing pellets bearing certain Fe and Zn amounts; such pellets were able to be retained for few hours by flotation in the highly acidic stomach cavity in order to favor and optimize the controlled release and gastrointestinal absorption of those essential trace elements.

7.2.2 Mechanisms of Action When Edible Clay Is Used

The mechanisms of action when edible clay is used could be as follows:

Protective action of the mucous membrane of the gastric wall and/or duodenum, since the covering or coating capacity of clay particles could avoid the action of chlorhydropeptic aggressive factors (Kikouama and Baldé 2010; and Young 2010).

Buffer and antacid action neutralizing the stomach excessive acidity; kaolinitic and smectitic clays having basic pH values are the most effective (Young 2010).

Releasing action in the stomach acidic medium of micronutrients (bioessential minerals), able to supplement the diet of deprived people (Hooda et al. 2004; and Kikouama 2008a, 2008b).

Restoration action of the hydro-electrolytic balance due to clay adsorption/absorption and cation exchange capacities, reason why clay-based medicines, such as Smecta® and Beidelix, constituted by dioctahedral smectites (*montmorillonite* and *beidellite*) are widely used against diarrhea, due to high sorption capacities of those clay minerals (Kikouama and Baldé 2010).

Reduction action of the pathogenic microorganisms and toxins fixed on clay particles and posterior removal by defecation.

7.3 Healing Clay for External or Topical Use: Mud Therapy and Pelotherapy

7.3.1 Background Data

Conceptually the so-called healing clay can be used for external or topical applications under the form of *clay/mineral water* paste on the affected skin sites, mixture named by the general and popular term *mud*, the clay component being defined as fine-grained and more or less plastic natural material containing both clay minerals and organic matter in variable amounts and the mineral water component having source in sea, lake, river, and spring (thermal or not thermal). Such mud can be called either *natural peloid* or *peloid s.s*. (meaning *peloid sensu stricto*) if therapeutic or cosmetic properties have been reckoned in it, either empirically or scientifically.

Teixeira 2015 presents an excellent report on the historical evolution of the use of *healing muds*. The author has considered 3 (three) stages or periods on that evolution, classified as:

1st – Mythological or mythological/empirical stage.
2nd – Clinical observation/empirical stage.
3rd – Scientific/research stage.

1st – Mythological or Mythological/Empirical Stage. This stage has prevailed mainly for very long periods of both Classic Antiquity and Middle Ages, and the mud health benefits were mainly attributed to the condescendency of some divinities.

The first report to the use of therapeutic mud is found in the "Lahoun or Lahun Papyrus" dated of nineteenth century B.C. In one of the six papyrus, the use of mud in the treatment of gynecological affections is reported, reason why this papyrus is known as the "*Lahoun gynecological papyrus*."

Hippocrates (460–377 B.C.) in his book *Treaty of Airs*, *Waters and Places* reports the use of *muds* and proposes their classification according to their therapeutic benefits.

Romans have used too *mud* for therapeutic purposes on both mythological and empiric basis. Pliny the Elder (24–79 A.C.) in his book *Naturalis Historia* reports the use of sea and river *muds* to treat wounds and tumors, the best results being mud achieved if mud was warmed up before application.

Dioscorides (c.41–90 A.C.) in his book *De Materia Medica* reports the use by Cleopatra of *mud* in which besides water milk and honey could be incorporated, as well as of *mud* from the sacred river Nilo.

During the Middle Ages, little is known about the use of thermal waters and muds in particular. However, in the Iberia Peninsula under the Arabian influence, Avicenna (980–1037) and Averroes (1126–1198) had emphasized the curative effects of seawater and mud.

Giovanni Dondi (1330–1388) from Padua in his book *De fontibus calidus agri Patavini* reports the use of warm mud (that he named fango, good for the treatment of skin affections) and water from Aqua Tabellicae Terme (called Aqua Augusta on the ruling of the emperor Augusto) and from Aqua Patavinae Terme (called Abano Terme since 1930).

Savonarola (1452–1498) from Florence was the author of a book entitled *De Balneis et Thermis* in which he reports the topical use of warm mud or fango to treat rheumatologic affections, and Margaret of Valois-Angoulême (Marguerite de Valois-Angoulême) (1492–1549) in her book *Heptaméron* reports the mud baths that were applied in the balneary of Cauterets located in Pirineus.

2nd – Clinical Observation/Empirical Stage. This stage is characterized by an attempt to explain the therapeutic qualities of both mineral waters and muds, and as so, it contemplates the clinical observation of the healing process and effects, stage that has an extraordinary development during Renaissance (fifteenth and sixteenth centuries) and thereafter up to the nineteenth century.

Andrea Bacci (1524–1600) in his book *De Thermis* published in 1571 report examples showing the importance of clinical evidences to explain the therapeutic benefits of muds particularly on rheumatic diseases.

Falloppio (1523–1562) in his book entitled *De Medicatis Aquis Atque de Fossilibus Tractatus* reports the mud application procedure: first cover with mud the affected area, second leave it to dry through exposure to solar radiation; or cover the affected area with renewed thin layers of mud. Later in the eighteenth and nineteenth centuries with both industrial and scientific revolutions, a renewed attempt was carried out in order to explain the therapeutic benefits of the applied mineral waters and muds based on muds' physicochemical and biological properties.

Several hydrotherapy centers have been built in Europe, particularly in Austria and German, although not directed by physicians, such as the Gräfenberg and the Norishopen hydrotherapy spas, the first directed by Priessnitz (1799–1851) and the second directed by the German priest Sebastian Kneipp (1821–1897). Priessnitz and Kneipp have been considered impostors due to the lack of medical background. Vincenz Priessnitz, an Austrian farmer, has been considered the founder of modern hydrotherapy, by promoting the use of water, particularly cold water, in alternative and orthodox medicine.

Kneipp cure consists of the interplay of hot and cold showers, stimulates blood flow, and strengthens the immune system. Little time afterward, the German priest Emanuel Felke (1856–1926) developed spas, first in Repelen and after in Bad Sobernheim, where the so-called Felke cure was practiced, including external applications of clay, warm and cold, under the form of wraps, poultices, compresses, and baths; the colder the clay, the more anti-inflammatory its effect; the warmer the clay, the more spasmolytic, circulatory stimulating, and relaxing its effect.

In the first half of the nineteenth century, in Europe, several spas have been built where the use of clay was a normal practice: Saint-Amand-les-Eaux, Dax, Aix-les-Bains, Bad Pilsen, Bad Nenndorf, Marienbad, Francesbad, and Karlsbad.

3rd – Scientific/Research Stage. This stage was initiated with the foundation of the first hydrology university clinic, in Vienna, by Winternitz (1835–1919) and with the publication in 1877 of *Die Hydrotherapie*. Since then, the healing properties of both mineral water and mud had been the object of studies based on scientific principles and methods.

Chemical, mineralogical, and thermal analyses became fundamental and decisive methods thoroughly used in the characterization of mineral waters and healing muds.

In the thermal resorts, the use of mineral water and mud could only be recommended and supervised by physicians specialized in medical hydrology or health resort medicine.

Few hundreds of scientific articles and few books and chapters of books have been published so far in reference journals on subjects related to healing muds, peloids, mud therapy, and peloidotherapy or pelotherapy, in general dealing with subjects related to mineralogy, chemistry (inorganic and organic), physics, physicochemistry, microbiology, toxicology, and medical and cosmetic applications.

Clay and mineral water of different typologies, individually or together as natural or artificial mixtures, have been thoroughly studied. Unfortunately, the real healing effects of peloids have been deficiently studied.

Healing muds are natural sediments to which, essentially on an empirical basis, therapeutic properties were attributed and to which various names are given in the various countries. For instance, in Portugal, the following names are used for mud: *lodo*, *limo*, *lama*, *vasa*, *argila*, and *barro*. Also, in other countries, various names are used for *healing mud*. To overcome the problem, the name *peloid* was first proposed in 1933 by Judd Lewis, president of the International Standard Measurements Committee, to encompass all those different names not having the same meaning.

There is information telling that the name *peloid* was first presented and discussed in 1931 in a meeting of the Directive Council of the ISMH (International Society of Medical Hydrology).

Notwithstanding the term *peloid* was officially adopted at the Conference of the ISMH held in 1938, in Wiesbaden, Germany. And, since then, as a rule, the terms *healing mud* and *mud therapy* have been replaced by the terms *peloid* and *pelotherapy*.

The International Society of Medical Hydrology and Climatology was founded in 1921. Since then, and periodically, international meetings had taken place. Portugal has been affiliated in this Society since 1936.

The article entitled "Peloids and Pelotherapy: Historical evolution, classification and glossary" (Gomes et al. 2013) is a review of the most significant changes and progresses that have taken place worldwide since 1938 in the field of pelotherapy. Also, according to Teixeira 2015, in Portugal, the first reference to healing muds was due to Pires da Silva (1662–?), who in his book *Chronographia medicinal das Caldas de Alafoens*, *offerecida ao Illustrissimo Senhor Duarte de Almeida & Sousa...*, published in 1696, reports the clinical effects and application techniques of waters and muds ("lodos," in Portuguese) (cit. Guimarães and Guimarães 1954).

Later the physician Francisco da Fonseca Henriques (1665–1731), also known as "Doutor Mirandela" in his book *Aquilegio Medicinal* published in 1726, presents the first register and description of the Portuguese hydrological resources having medicinal virtues (caldas, springs, rivers, lakes, etc.) and in Chap. 1 entitled "Das

Caldas," in regard to Caldas da Quinta das Flores where the Hospital Real das Caldas was built, mentions the existence of a mud (lodo) good to treat joint inflammation, if applied warm.

The Hospital Real das Caldas was rebuilt by king D. João V and changed its name to Hospital Termal das Caldas da Rainha. In the new hospital, the king ordered the construction of 7 (seven) tanks for mud-bathing. This practice was few years later retaken and developed by the physician Francisco Tavares, professor at the University of Coimbra and considered the founder of the modern hydrology in Portugal, who wrote two books entitled *Advertências sobre os abusos e legítimo uso das Águas Mineraes das Caldas da Rainha* (1791) and *Instruções e Cautelas Practicas sobre a natureza*, *diferentes species*, *virtudes em geral e uso legítimo das águas mineraes*, *principalmente das Caldas da Rainha* (1810). The second book was divided into two parts: in the first part entitled "*Da natureza*, *divisões*, *e virtudes das águas…*," mineral waters are defined, and their characteristics and therapeutic indications are presented too; in the second part entitled "*Do uso médico das águas das Caldas*," the utilization techniques and treatments duration are described, and in a specific chapter entitled "*Dos modos de aplicação das águas*, *do banho*, *embrocação*, *lodo*, *clister*, *vapor*, *bebida*," the use of mud (lodo) is dealt with.

In the second half of the nineteenth century, the use of *healing muds* (*lamas curativas*, in Portuguese), whose health benefits are mainly reckoned on an empirical basis, has deserved more and more attention and concern, reason why since then the physicochemical properties of water and mud were determined and their use in spas was recommended and controlled by medical hydrologists.

In Termas dos Cucos, in Torres Vedras, on May 15, 1893, a balneary was built for the indoors use of *mud* ("*lama*") applications. This balneary has replaced the outdoors *mud baths* taken in the fine-grained and warm sediments called "nateiros" deposited on the right bank of river Sizandro. The sediment was transported suspended in the water that after undergoing deep circulation has ascended through carbonate and evaporitic rocks and emerged along a fault zone as artesian springs. At the emergence sites, the water temperature measures around 40 °C.

The healing mud or natural peloid from Vale de Cucos was collected at a rare renewable mineral deposit. Every year around 6–7 metric tons of *mud* was collected in order to be used in the spa. Gomes 2002 reports relevant data on the local geology, as well as on mineralogy and chemistry of the mud from Vale de Cucos that, at that time, was maturated during about 6 months in an outdoors tank located nearby the balneary. The maturation process was an attempt to beneficiate the properties of the healing mud.

Cucos's thermal water is classified as chloride, bicarbonate, sulfate, and lithic. Cucos's *mud* has a complex mineral composition, the clay fraction being composed of the clay minerals illite, kaolinite, chlorite, and smectite, associated with the non-clay minerals calcite, quartz, and non-identified sulfides.

Cucos's *mud* chemical composition is as follows: SiO_2, 38.49%; Al_2O_3, 17.21%; TiO_2, 0.75%; Fe_2O_3, 5.15%; MnO, 0.08%; CaO, 17.21%; MgO, 2.61%; K_2O, 2.57%; Na_2O, 0.91%; P_2O_5, 0.13%; CO_2, 13%; SO_3, 0.58%; and H_2O, 5.04%.

In Termas de Cucos, water baths and mud baths were taken at 38–39 °C, and mud poultices were applied at 43–45 °C. Rheumatoid arthritis, psoriatic arthritis, extra-articular rheumatism, arthrosis of various types, and ankylosing spondylitis were the main disorders treated in Termas dos Cucos. At the beginning of the twenty-first century, Termas dos Cucos, most probably due to natural degradation of the facilities, and also due to sanitary safety reasons, was disactivated.

In Termas das Furnas, in São Miguel's island of the Azores archipelago, sulfurous warm dark-gray mud was used for the treatment of rheumatic disorders, in particular. Mud was formed from the interaction of volcanic hydrothermal boiling acid water (pH = 2–3) with the underground lying alkali-feldspar syenite.

The chemical analysis of Furnas's mud is as follows: SiO_2, 48.56%; Al_2O_3, 28.14%; TiO_2, 1.18%; Fe_2O_3, 2.38%; MnO, 0.05%; CaO, 0.24%; MgO, 1.02%; K_2O, 2.41%; Na_2O, 0.84%; P_2O_5, 0.19%; SO_3, 1.86%; and I.L, 11.86%.

Termas das Furnas has been disactivated too in the beginning of the actual century. Also, in Caldas de Vizela, partial baths of mud with source in the Aveiro lagoon were practiced till the end of the last century, being assumed that the discontinuity was due to sanitary safety reasons. Preferentially treatments would involve the limbs of the body, arms, and legs, suffering from rheumatic affections.

Presently, in Portugal, there are 41 (forty-one) still active thermal spas, but in none of them, muds/peloids produced in the country are used for either therapeutic or cosmetic purposes. However, the traditional practice outdoors of mud therapy on an empirical basis still persists in certain natural sites of the littoral Atlantic of Portugal, more precisely at the beaches named Consolação, Parede, Meco, and Porto de Mós, where clay/water pastes prepared by mixing marly clay extracted from the nearby cliff with sweater are used for the treatment of rheumatic and skin affections (Gomes 2002; Cardoso-Gomes and Gomes 2015). In all cases, the treatment follows the same methodology. After coating or covering the affected areas of the body with the clay paste that has been just prepared, it is exposed to solar radiation for 15–20 minutes, time sufficient to get it dried; and afterward, the layer or film of applied paste is washed out with seawater.

Clay and the quasi-amorphous or amorphous inorganic materials and the organic materials both currently associated with it constitute good support and vehicle for fixation, growth, and transportation of organic colloids and microorganisms (bacteria and fungi, some eventually pathogenic) and for fixation of chemical elements, some potentially toxic, naturally existing or that could be introduced into the occurrence environment, reason why the sanitary safety control both chemical and microbiological of *healing clay* (both *edible clay* and *mud/peloid*) should be a prerequisite before its use.

Within all constituents of *healing mud/peloid*, clay is the most common constituent and is the one most studied. Such is particularly true for *natural peloid* also called *primary peloid* or *primitive peloid*, as well as for *peloid s.s.*, or *peloid sensu stricto*, or just called *peloid*.

Both *natural peloids* and *peloids s.s.* are usually classified into three typologies: the so-called essentially inorganic peloids, the so-called essentially organic peloids, and the *mixed inorganic/organic peloids*.

Natural peloid is naturally maturated and applied at or nearby the natural site of occurrence, and its therapeutic interest is mostly based on empirical evidences; otherwise, the therapeutic interest for *peloid s.s.*, a healing mud or muddy suspension that is artificialized through manipulation comprising refining and beneficiation and maturation in an artificial environment and appropriate conditions, is based on scientific evidences, and it is applied under medical prescription and surveillance inside *spas* or other health-care facilities (Gomes et al. 2013).

Special types of clay (such as kaolin and bentonite) and of mineral water (such as seawater and spring natural mineral water) are the two main constituents of *designed and engineered peloid*, a particular type of *peloid sensu stricto or peloid s.s.* (Gomes 2015).

As fundamental constituents of *peloids*, the semi-solid pastes produced by mixing particular types of clay, characterized by simple mineralogical and chemical compositions, and mineral water, previously and individually characterized mineralogically, chemically, and microbiologically, have been thoroughly studied. Less studied has been the interaction between clay and mineral water, particularly what changes happen in the liquid phase after the mixture and interaction of both solid and liquid phases.

It is worth mentioning the publication of Carter 2002, among the many works that have been published on this subject in recent years, given its relevance and because it is an important synthesis work. Indeed, this publication systematically highlights the beneficial effects of clay minerals on human health, whether in the form of external or topical applications (cataplasms, mud baths, cosmetics, etc.) or in the form of participating in the formulations of many drugs, as principles or as excipients.

Natural peloids as well as peloids s.s., of either medical or cosmetic grade, could be applied directly onto the skin, as *mud packs* or *peloid packs*, for instance, on joints (of knee and hand) or on backbone regions. Just before its application that, as a rule, lasts 20–30 minutes, both *healing mud* and *medical* or *therapeutic peloid* could be heated up to about 45–50 °C, and the heat promoting the opening of skin pores facilitates the transdermal absorption of both beneficial and hazardous substances contained in the peloid.

Healing muds and peloids could be also used in the form of compresses. Immediately before application, both *healing mud compress* and *peloid compress* could also be warmed up to about 45–50 °C using a microwave oven. However, these days both mud and peloid packs can be kept at constant temperature for longer times than the usual 10 minutes that the temperature of the pack takes to go down from 45–50 °C to the body normal temperature of 37 °C, in case the pack is covered with an appropriate thermic mat.

Potentially toxic elements (heavy metals included) are always present in variable contents both in the so-called natural peloid and in the *peloid s.s.* As said above, there is a lack of normative regulation for the quality and safety of the raw materials that constitute both *natural peloid* and *peloid s.s.* or simply *peloid*.

In fact, in general, with regard to quality criteria and regulations, there are no effective chemical constraints for both *peloid* types used for therapeutic applications. On the contrary for cosmetic products (in which *cosmetic peloids* could be included), there are highly restrictive chemical constraints, situation well exemplified in the European Directive (76/768/ECC) stating that elements such as Hg, Cd, Pb, Sb, As, and Se should not be present or in case of being present only extremely low contents (around 1 ppm) should be admitted.

Mud therapy and peloid therapy, both under the comprehensive name *pelotherapy*, are reckoned as being potential efficient means to treat muscular-skeletal affections due to the action of a double process: *thermotherapy* and *chemotherapy*.

As aforesaid, *mud* and *peloid* are particularly distinguished because *mud* also called *natural peloid* or *primary peloid* is maturated in the natural environment, whereas *secondary peloid* or *peloid s.s.* or yet simply *peloid* is maturated in an artificial environment, for instance, inside the *spa* facilities. Literature mentions maturation times with durations from 2 to 6 months. There have been studies about the peloid changes taking place during maturation, but no studies have demonstrated the therapeutic efficacy gained from peloid maturation.

Microbiological control for sanitary safety, particularly of pathogenic microorganisms, is essential along the processes of preparation, storage, application, and reuse of both *healing mud* and *peloid*. Naturally, *healing mud* and *peloid* with origin in sedimentary deposits, due to the possibility of bearing higher contents of organic matter, are more susceptible to microbiological contamination compared to *mud* and *peloid* with origin in volcanic deposits.

Dermal absorption is the natural pathway for microbial infection due to *healing mud* or *peloid* topical application; hence, the skin areas under treatment should be healthy, i.e., without "*entrance doors*." A particular concern in regard to the presence in *healing mud* and *peloid* of potentially hazardous microorganisms (bacteria and fungi) has been reported by various authors such as Mpuchane et al. 2010; Bisi-Johnson et al. 2010; Okunlola and Owoyemi 2011; and Bisi-Johnson et al. 2013.

In the European Union, there are no uniform rules for the microbiological specifications of *healing muds* and *peloids*, despite the concern shown by the European Spas Association (ESA). In its General Assembly held in 2006 in the Thermal Resort São Pedro do Sul, in Portugal, ESA had considered and proposed quality criteria for *spring medicinal waters* and *thermal peloids* but has not quantitatively defined the minimum requirements or guidelines, both chemical and microbiological, for both *spring medicinal water* and *healing mud/peloid* used in balneology (the study and therapeutic use of *mineral-medicinal waters* and of *healing mud/peloid*).

If *medical peloids* are considered equivalent to remedies or medicines, they should not contain pathogenic microorganisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, *Escherichia coli*, and *fecal coliforms*, among others. In regard to the pathogenic germs of anthropogenic origin *Escherichia coli* and coliform bacteria that could be present in the liquid phase extracted from *mud/peloid*, ESA established the guide value of 100 CFU (colony-forming units)/100 ml and the limit of 2000 CFU/100 ml for *Escherichia coli* and the guide value of 500 CFU/100 ml and the limit of 10,000 CFU/100 ml for coliform bacteria. Also, in regard to microbial quality and quantity, the normative limits proposed by

European legislation (EP 7.0, 2011) could be applied to clay-based natural products used for therapeutic purposes, such as *edible clays* and *peloids*. The limit for total aerobic microbial count is 10^3CFU/g in "non-sterile substances for pharmaceutical use," and for "non-sterile oral dosage forms containing raw materials of natural (animal, vegetal, or mineral) origin," the limit is 10^4CFU/g. The pathogen microorganisms *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella* spp., and *Staphylococcus aureus* should be absent.

Both negative and positive effects on human health of healing and edible clays are matter of concern and study of the emerging scientific field of medical geology that assesses the complex relationships between geo-environmental factors and their impacts (beneficial or toxic) on humans and looks at the understanding of the mobility (through natural and anthropogenic processes), bioavailability, bioaccessibility, exposure, and transfer mechanisms and processes to humans of geogenic metals and metalloids as well as their ecotoxicological impacts and health effects.

According to Davies et al. 2004, and Skinner 2007, the intake and incorporation of geogenic elements could follow three processes: dermal absorption via mud baths or bathing in geothermal water; ingestion of water, food, and soil/clay (either intended, geophagy, or unintended); and inhalation of atmospheric dust and aerosols.

Medical geology is a transdisciplinary scientific field that requires an integrated involvement and cooperation of specialists in geology, mineralogy, geochemistry, hydrochemistry, environment, toxicology, epidemiology, and public health.

One review dealing essentially with basic concepts as well as with the benefits and risks of using *healing clay* for health and skin care will be hereunder disclosed.

7.3.2 Basic Concepts of Materials and Therapeutic Techniques Involving the Use of Healing Muds and Peloids

Mud – From a sedimentological point of view, mud is a geologic field term for any soft and wet silt-clay mixture of sedimentary or volcanic origin with more than 50% of its size fraction smaller than 63 μm and that can exhibit higher or less plasticity mainly depending on the weight ratio of both clay and mineral water: seawater, river water, lake water, spring water, hydrothermal water, etc.

As a natural product of geological and/or biological processes, *mud* composition could be essentially inorganic, or essentially organic, or yet mixed inorganic/organic. As a popular term, mud means a non-consolidate fine-grained sticky or slimy sediment of any origin. Mud can also be clay or carbonate-rich sediment that normally contains some silt-sized components and organic material. Mud can also be defined as a semi-solid mixture of mineral matter and organic matter with mineral water in variable amounts. Occasionally mud properties can be relevant for *healing* purposes, based on empirical or medical and clinical evidence.

Depending upon its origin and composition, several typologies and designations could be attributed to healing mud*: bioglea mud* or *biofilm mud* (called *barégine* in France and *muffe* in Italy); *estuary mud*; *lagoon mud*; *freshwater lake mud*; *gyttja* or *"nekron" mud*; *peat mud*; *river mud*; *salinas* or *salt pan mud*; *salt lake mud*; *sapropel mud*; *sea* or *marine mud*; *thermal spring mud*; and *volcanic mud*.

The names of the very singular *natural sediment* from which *healing mud* is derived change with the idioms of the countries, and derived or not from the Latin, as follows: *argilla*, *limus*, *lutum*, *lamae*, and *caeum* (in Latin); *argila*, *barro*, *greda*, *lama*, *lodo*, *limo*, *vasa*, *silte*, *sapropel*, *turfa*, and *biofilme* (in Portuguese); *arcilla*, *barro*, *greda*, *cieno*, *lama*, *lodo*, *fango*, *limo*, *vasa*, *silte*, *sapropelli*, *turba*, and *bioglea* (in Spanish); *argile*, *boue*, *glaise*, *fange*, *liman*, *limon*, *silt*, *vase*, *sapropeli*, *tourbe*, *muffe*, *mousse*, *barégine*, *bioglée*, and *gyttja* (in French); *argille*, *fango*, *limi*, *muffe*, and *torbe* (in Italian); *clay*, *mud*, *mire*, *slime*, *ooze*, *loam*, *silt*, *sapropel*, *turf*, *moor*, *peat*, *biofilm* or *bioglea*, and *gyttja* (in English); *ton*, *schlick*, *schlamm*, and *torf* (in German); and *tîn* and *hama* (in Arab).

The designation *thermal mud* is attributed to *mud* with origin and deposition related to thermal springs that at their sources the water exhibits temperatures significantly higher relative to local air temperatures.

Healing mud – *Mud* to which empirically or even medically had been recognized and attributed healing properties, both therapeutic and cosmetic, and that it is topically used without previous manipulation at or nearby the natural occurrence site. The term *healing mud* is in this book equivalent to the term *natural peloid*.

Mud therapy – The topical use of mud, i.e., natural muddy sediment, under the form of mud paste, thicker or thinner, for therapeutic and/or cosmetic purposes, mostly on an empiric way and, as a rule, without medical counselling and surveillance. Such natural muddy sediment that has been maturated in the geologic site where it occurs is simply called *healing mud*.

The use of mud for health-care purposes goes back to prehistory. Egyptians have used muddy sediments from the river Nilo, under the form of topical applications, to treat disorders of the feminine genital system and to treat skin burns. Romans were the first to recommend *mud baths* for therapeutic purposes, mud having origin in deposits occurring at the bottom of seas, lakes, and rivers (case of Danube) as well as in peat from marshlands.

In France, before Roman occupation, mud baths were practiced in the so-called thermal stations of Dax (Aquitaine), Balaruc (Hérault), and Saint-Amand (Nord), and after Roman occupation, these and other stations were much developed becoming quite prosperous. The barbarian invasions in Europe significantly diminished the prosperity of the thermal stations, and only in the Middle Ages, the balneal activity could be recuperated.

Since Renaissance, at the final of the fifteenth century, in Italy, the thermalism and the use of *warm mud* became popular, particularly in resorts located in the Euganean basin, famous for *thermal springs* and *thermal muds* locally called *fangos*.

Many documents exist reporting the application of *warm mud* washed out with thermal water when mud application was finished.

Fig. 7.2a and 7.2b Mud application, sea water being the liquid phase, used to treat rheumatic disorders at Parede's beach (on the left); and for skin care purposes at the Porto de Mós's beach (on the right)

In Europe, several countries such as Germany, Italy, Romania, Hungary, Greece, Spain, and Russia have used *mud* for therapeutic purposes before and after Roman occupation, and they are still using it.

Soon public conscience of eventual sanitary risks related to malpractices of hygiene lead to the replacement of *collective mud baths* for *individual mud baths* and the replacement of *general mud baths* involving almost all body for *localized mud baths* involving parts of the body, such as leg and arm.

Good example of *mud therapy* is the traditional practice in certain natural sites of the littoral Atlantic of Portugal, more precisely at the beaches named Consolação, Parede, Meco, and Porto de Mós, involving the empiric use of mud, more precisely of clay pastes made by mixing marly clay extracted from the nearby cliff with sweater, for the treatment of rheumatic and skin affections (Gomes 2002; Cardoso-Gomes and Gomes 2015).

Figure 7.2a, b show *mud application* at the beach of Parede, near Lisbon, and at the beach of Porto de Mós, in Algarve. Also, *mud baths* are taking place in the discontinued salt pan named Barquinha, in Castro Marim, in Algarve, using the *saline mud* deposited at the bottom of the salt pan.

Peloid – The name *peloid* corresponds to the name *péloïde* proposed in 1933 by Judd Lewis, president of the International Standard Measurements Committee, to encompass all the diverse names of natural sediments to which therapeutic properties were attributed, names naturally varied from country to country. Lewis (1933) defined peloid as "Any natural product composed of a uniform mixture of finely divided organic and inorganic matter with water and applicable in medical practice as cataplasm for external treatment."

For essentially inorganic natural sediments deposited around springs, the names *boue*, *fango*, *schlamm*, *lama*, and *barro* are employed in France, Italy, Germany, Portugal, and Spain, respectively.

The name *peloid* is derived from the Greek word "πξλος" spelled "pelòs," meaning "mud," and from the name *peloid*, the terms *peloid therapy* and *pelotherapy* (in short) were derived. The designation *peloid* was definitively adopted at the Conference of the ISMH (International Society of Medical Hydrology) held in Wiesbaden, Germany, in 1938.

Then, *peloid* was defined as "Natural product (natural sediment) composed of a mixture of mineral water (seawater and lake water included) with organic or inorganic matter that results from either geologic or biologic processes or yet from both processes, and is utilized for therapeutic purposes under the form of packs, compresses or baths."

This is the official *International Definition of Peloid* that was approved in the IV$^{\text{ème}}$ ISMH Conference held in 1949, in Dax, France. Dax is the first and principal thermal town in France that is frequented by about 55,000 patients/year.

The famous *peloid* of Dax, named Terdax®, is produced by mixing the "limon," a clay-rich sediment extracted from the alluvium of Adour river at 2–8 m deep refined by sieving to less than 800 μm with about 43% water, with the hyperthermal (39–44 °C) calcic and sodic chloride-sulfate natural mineral water that emerges from a local thermal spring. Locally cultivated algae (*Cyanophyceae*) and bacteria (*Clostridium bifermentans*, of the sulfur cycle) are added to the mixture that undergoes maturation inside one hermetic container during 21 days. In 2005, the production of Terdax® was estimated at 260,000 ton/year to be supplied to the 16 thermal establishments existing in Dax (Francois et al. 2005).

Also, the official *International Classification of Peloids* (the original, in French, is shown in Table 7.1) was established and approved at the same ISMH Conference aforesaid referred to, based on:

1. Origin of the solid component.
2. Chemical nature and temperature of mineral water.
3. Maturation conditions.

Before and after 1949, various authors have proposed definitions and classifications for *peloids*, since concepts and classifications can change with time, situation justified on the output of the progressive scientific evolution. Porlezza 1965 reports the various definitions of *peloid* being proposed in the time interval 1933–1952.

Gomes et al. 2013, show the historical evolution of *peloid definition* and of *peloids classification* too, and the authors have proposed a new definition of *peloid* as follows:

> *Peloid is a maturated mud or muddy dispersion with healing and/or cosmetic properties, composed of a complex mixture of fine-grained natural materials of geologic and/or biologic origins, mineral water or sea water, and commonly organic compounds from biological metabolic activity.*

The above-proposed definition was the outcome of discussion within an *ad hoc Working Group* which gathered researchers from different scientific fields: medicine, pharmacy, physics, geology, chemistry, biology, and medical hydrology. Such Working Group also proposed a classification of peloids into two main classes, *natural peloids* and *peloids* sensu stricto or *peloids s.s.*, the first comprising muds and muddy suspensions naturally maturated at the sites where they occur and the

Table 7.1 Original international classification de Péloïdes (Dax, 1949)

Dénomination des péloïdes	Origine	Eau minéral		Conditions de maturation
		Nature chimique	Température	
Boues (Fanghi, muds, schlamm)	A prédominance inorganique (minérale)	Sulfureuse, sulfatée, chlorurée, bromurée, iodurée	Hyperthermale *au griffon*	(a) in situ (Sur le *griffon* des sources)
			Homéothermale (36–38 °C) *au griffon*	(b) *En bassin*
			Hypothermale *au griffon*	
Limons	*Id.*	Eau de mer ou de lac salé	Hyperthermale *au bassin*	In situ
Tourbes (Torbe, peats, moor)	A prédominance organique	Alcaline, carbonatée, ferrugineuse, sulfureuse	Hyperthermale *au griffon*	(a) Ouverte
			Homéothermale *au griffon*	(b) Couverte
		Eau de mer	Hypothermale *au griffon*	
			Hypothermale *au bassin*	
Muffe (mousses, barégines)	*Id.*	Sulfureuse	Hyperthermale *au griffon*	In situ
Bioglées Autres que le muffe (algues, etc.)	*Id.*	Eaux minérales autres que les eaux sulfureuses	Hyperthermale *au griffon*	*Id.*
			Homéothermale *au griffon*	
			Hypothermale *au griffon*	
Sapropeli	Mixte	Alcaline, ferrugineuse, sulfureuse	Hypothermale *au bassin*	*Id.*
Gyttja	*Id.*	Eau de mer	*Id.*	*Id.*

Note: *Limon*, muddy sediment predominantly inorganic, such as loam, slime, and ooze that are deposited by sea, lake, or river waters; *Muffe*, muddy organic sediment rich in filamentous bacteria, known as bioglea or biofilm that is formed on dependence of sulfurous mineral water; *Bioglée*, muddy organic-rich sediment known as bioglea or biofilm that is formed on dependence of non-sulfurous mineral water; sur le *griffon* des sources, on the spring of the sources; *Gyttja*, Swedish term for organic-rich freshwater mud, which is a mixed organic-rich mud that is rapidly accumulated in eutrophic lakes; the organic component that makes up to 40% of the dry mass results from the partially anaerobic putrefaction of plankton; it is a unique geological formation occurring at the bottom of water bodies mostly in overgrowing, eutrophic lakes (Vincevica-Gaile and Stankevica, 2008)

second comprising muds and muddy suspensions maturated inside spa facilities or research laboratories in conditions that could enable modifications of natural peloid relevant properties.

Peloids s.s. could encompass either the introduction in their composition of natural or synthetic functional additives or even the development in the laboratory of formulations still based on mixtures of a natural solid phase (for instance, a specific clay) with a natural liquid phase (for instance, a specific mineral water).

Nature and origin of *natural peloids* are diverse: volcanic and sulfur-rich mud (for instance, in Vulcano island, Aeolian archipelago, Sicily, Italy; in Copahue, Neuquen, Argentine; and in Caldeiras da Ribeira Grande, São Miguel island, the Azores archipelago, Portugal), saline mud (for instance, in Sečovlje, Slovenia), organic-rich mud (for instance, the black mud of Peruibe, Brazil, and the black mud from Dead Sea, Israel), and peat mud (for instance, the peat of Neydharting, Austria, and the peat of Massaciuccoli Lake, Lucca, Italy).

Clay minerals, which are hydrous phyllosilicates, being as a rule associated with other minerals (mainly carbonates, sulfides, and other silicates) and organic compounds, are the major constituents of peloids' solid phase. On the other hand, peloid's liquid phase, as a rule, could be fresh water from river and lake; natural mineral water from deep-seated wells and from natural springs, either thermal or not thermal; and yet seawater.

Peloids' gas phase, as a rule, is one or more than one of the following natural gases: CO_2, H_2S, SO_2, CH_4, and Rn.

Maturation is an essential but complex and multifactorial process that depends upon maturation time, stirring method, temperature, and light exposure. Maturation would provide matter exchanges between *peloid solid*, *liquid*, and *gas phases* as long as the physical, chemical, and biochemical equilibrium could be attained. Maturation could be also a creative process particularly if the thermal mud bears organic matter and thermophilic microorganisms, since along the process changes in the initial existing microflora and the production of anti-inflammatory compounds (e.g., sulfoglycolipids) could take place (Galzigna et al. 1995, 1996, 1998, 1999a, b; Tolomio et al. 1999, 2002, 2004; and Centini et al. 2015).

The time during which the maturation process develops can range from few months to years (Fernández-Gonzalez et al. 2013). Maturation induces physical and chemical changes in both solid and liquid phases of the peloid due to mutual interactions. Maturation progress can be followed on the basis of the changes on mud organic composition and antioxidant properties acquired along the time (Centini et al. 2015). Also, during maturation, new microorganisms could be developed able to enrich the peloid with therapeutically active compounds from the secretion of metabolic products (Veniale et al. 2007; Quintela et al. 2012; and Gomes et al. 2013). As a matter of fact, during maturation, *peloids* could be progressively colonized by thermophilic microorganisms, mainly *Cyanobacteria*, green algae, and diatoms (Andreoli and Rascio 1975; Sanchez et al. 2002; Tolomio et al. 2002, 2004; and Quintela et al. 2012).

Pesciaroli et al. 2016, have studied the bacterial community developed during the maturation of a therapeutic mud. The authors have used cultivation-independent methods, and next-generation sequencing techniques were used to compare bacterial diversity and community structure in peloids at different stages of maturation and to determine the microbiological changes that occurred during the maturation

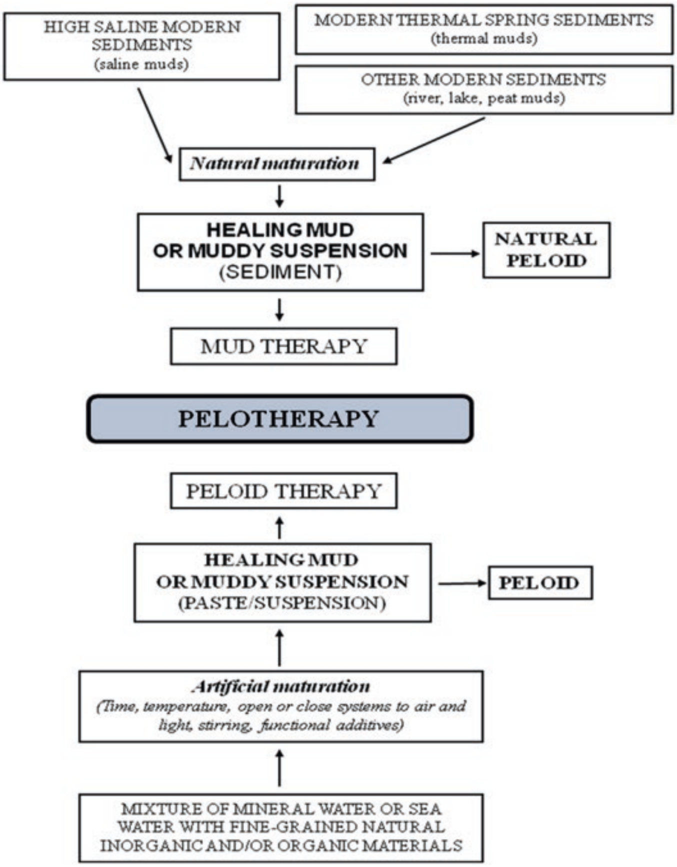


Fig. 7.3 Concepts of *mud* or *natural peloid*, *mud therapy*, *peloid*, and *peloido therapy* or *pelotherapy*. (Source: Gomes et al. 2013)

process. The obtained results showed great differences between the microbiota present in peloid samples and in the thermal waters used in their preparation. Also, important changes were found in the microbial populations during the early stages of maturation, but after 3 months of maturation, the changes became minimal indicating the stabilization of the system.

Peloid therapy – The topical use of natural muddy sediment under the form of mud paste for therapeutic and/or cosmetic purposes, under medical counselling and surveillance, sediment that besides maturation in the occurrence site has undergone later manipulation and maturation in the artificial environment existing inside the *spas* of both thermal resorts and thalassotherapy centers. Such artificialized natural muddy sediment is simply called *peloid s.s*. or simply *peloid*.

In France, in 2005, in a total of 94 thermal stations, 73 used *maturated muds* or *peloids* for therapeutic and cosmetic purposes (François et al. 2005).

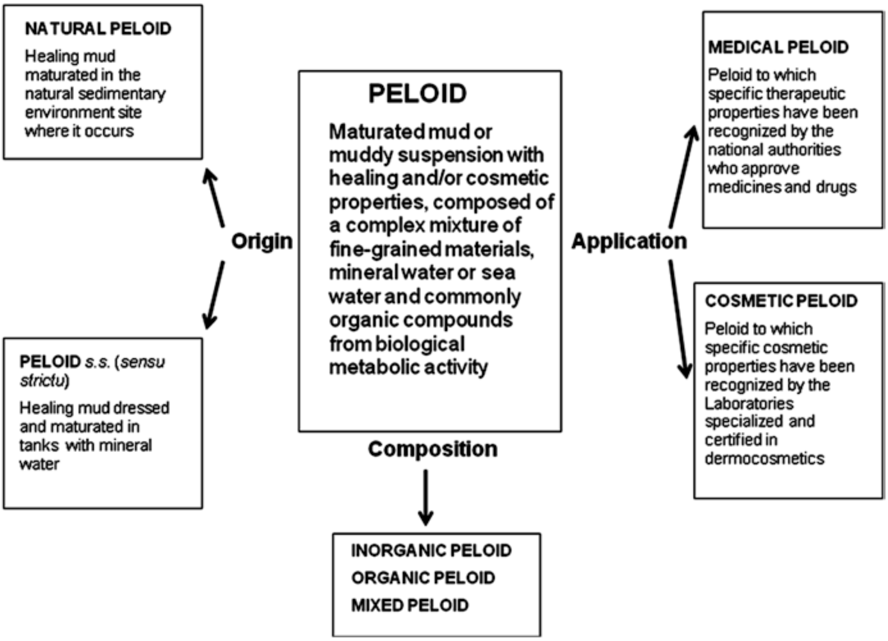


Fig. 7.4 Concepts of *natural peloid*, *peloid s.s*, *peloid*, *medical peloid* and *cosmetic peloid*. (Source: Gomes et al. 2013)

Pelotherapy – Term of comprehensive meaning applied to the use of either *healing mud* or *natural peloid* or yet of *peloid s.s.* or just *peloid* for topical applications with therapeutic or cosmetic purposes (see Figs. 7.3 and 7.4). Pelotherapy is applied all over the Europe, particularly in thermal, thalassotherapy, and rehabilitation centers, to treat specific rheumatological and dermatological pathologies.

Maraver 2006; Gomes et al. 2013; and Horno 2014 report in a synthetic way relevant data concerned with the historical evolution of *pelotherapy*. Mud or natural peloid can be applied either outdoors (at or nearby the natural occurrence site) or indoors of nearby or faraway *spas* where it could get the designation *therapeutic mud* or even *peloid* if the original mud had undergone some manipulation involving refining and beneficiation, situation exemplified in the case of the Dead Sea sulfur-containing mud enriched in magnesium salts known and commercialized worldwide due to its therapeutic and cosmetic properties (Harari 2012a, 2012b; Abu-Shakra et al. 2014; and Ma'or et al. 2015).

Fangotherapy – It is a particular type of *pelotherapy* that involves the use of *fango* (name of Italian origin attributed to *healing muds* or *natural peloids* deposited from thermal springs, particularly sulfur-bearing springs, as happens in the case of the Euganean volcanic region, in Italy, where important thermal resorts do exist, such as Montecatini, Abano, and Battaglia Terme).

Baschini et al. 2018, are the authors of a chapter of the book entitled *Copahue: La Ciencia, Lo Magico y El Arte de Curar* (Soria CM, Vela ML, and Jalil ME, editors) dealing with the physical and chemical properties of the *fangos* deposited in the unique Geothermal System of Copahue, *fangos* which are utilized at the Thermal Centre of Copahue, in the Neuquen Province of Argentine Patagonia, the most interesting and important in all America and maybe in the world. Such *natural peloids* could become *peloids s.s.* or simply *peloids*, after undergoing manipulation and maturation (process that lasts weeks or months and is needed to achieve the physicochemical equilibrium between *peloid* solid, liquid, and gas phases) inside the *spas*.

The Euganeo thermalism is known since few millennia ago. Euganeo Caldara 2017, issued by Fondazione Cassa di Risparmio di Padova e Rovigo, synthetically describes "Il Sistema Termale Euganeo." The thermal water of the Euganean basin is part of an underground hydraulic system with origin in the Dolomites mountain in the Venezia region. The water of meteoric origin penetrates the rocks and goes down to 2500–3000 m deep being progressively heated and mineralized (in chlorine, iodine, and bromine) and rapidly uprises as hyperthermal (about 85 °C) in the Euganean basin, being utilized in several thermal centers, such as Abano Terme, Battaglia Terme, Montegrotto Terme, and Galzignano Terme. These thermal mineral waters are used in the natural maturation process of fango allowing the growth of micro-algae with pharmacologic interest. Inside the facilities of the thermal centers, this *virgin fango* could be matured after being put in a long-lasting contact with the thermal water in artificially controlled conditions, providing as so curative specificities to its three constituents:

1. Thermal water characterized by its specific temperature and chemical composition.
2. Mineral component characterized by its mineral and chemical composition.
3. Biological component developed during the maturation process.

The "Centro Studi Termali Pietro d'Abano, CSTPdA," with headquarters in the University of Padua, provides the necessary scientific and technical support for the therapeutic use of *fango* from the Euganean basin.

Natural peloid – In general, it is a natural muddy sedimentary geomaterial of marine, fluvial, estuarine, lacustrine, or volcanic origin, characterized by a complex composition, consisting of a mixture of solid, liquid, and gas phases, each one containing diverse and specific components. Depending upon *natural peloid* origin and composition, the *peloid liquid phase* could represent around 30% to 90% of the *peloid weight*, the lowest values corresponding to peloids rich in mineral matter and the highest values corresponding to peloids rich in organic matter.

Based on origin, *natural peloids* can be classified into two classes:

1. *Primary peloids* or *virgin peloids* if the solid component has been mechanically transported as particulate dispersed material in the mineral water of a spring and thereafter it is deposited.
2. *Secondary peloids* if the solid component and the mineral water come from different sources (Veniale 1998).

Also based on origin, the designations *eupeloids* and *parapeloids* have been used for *natural peloids* and *artificialized peloids*, respectively. Based yet on global composition, more precisely on the quantitative ratio inorganic/organic components, *natural peloids* are classified into three main groups (Gomes, 2010):

1. *Essentially inorganic peloids* (e.g., healing mud, fango).
2. *Essentially organic peloids* (e.g., biofilm).
3. *Mixed inorganic/organic peloids* (e.g., peat, sapropel, gyttja).

Still based on both mineral and chemical composition of *natural peloids*, Pozo et al. 2010, classified them into three groups:

1. *Phyllo-peloids* characterized by significant content of phyllosilicates represented by clay minerals.
2. *Organo-peloids* characterized by significant participation of organic matter.
3. *Sulfo-peloids* characterized by significant participation of sulfur existing in both organic matter and mineral waters, under the forms of S, H_2S, or metal sulfides.

If yet based upon their application and function, *natural peloids* can be classified into two groups (Gomes et al. 2013):

1. *Therapeutic peloids* or *medical peloids*.
2. *Cosmetic peloids*.

All the classifications referred to could be applied as well to *manipulated and modified peloids,* which are derived from *natural peloids* after undergoing manipulation, modification, and maturation inside *spa* facilities.

In terms of health safety, both *natural peloids* and *manipulated and modified peloids* could be hazardous due to the difficult chemical and microbiological control of peloids' major constituents, clayey material and mineral water, which could cause potential health risks. Any eventual chemical toxicity found in these peloids could be attributed to the presence of toxic chemical elements such as Hg, Pb, Sb, Cd, Zn, Cu, and Se, as well as to radioactive elements, the toxicity depending on concentrations and bioavailability. Some studies have considered the possible toxicity of peloids based on chemical analyses of both solid and liquid phases (Baschini et al. 2010; Rossi et al. 2013; Quintela et al. 2010, 2012, 2015; Glavas et al. 2017; and Díaz Rizo et al. 2018).

There are no established official regulations about peloids' chemical safety. However, the academics use to follow the reference values indicated in US Pharmacopeias, considering that peloids have similarities to pharmaceuticals, in the European regulation for cosmetic products, in the EMA (European Medicines Agency 2008), and in Health Canada (2012).

As important as the chemical safety is the sanitary safety. Within the European countries, with exception of certain regions of Germany and France, there are no quality standards or guidelines for muds or for peloids utilized for therapeutic purposes. In what microbiological risks are concerned, besides its *autochthonous or natural* microflora, *natural peloids* could have an *allochthonous microflora* of great importance as they may include undesirable pathogen microorganisms, most of anthropogenic origin.

Recently Gerencsér 2014 has assessed the microbiological risk of five *natural peloids* occurring in the Carpathian basin which are certified and marketed in Hungary, country where balneology is of paramount importance. The famous Héviz's *peloid* registered as "Neydharting" *peloid* was one of the *natural peloids* being studied and classified as *peat* due to its high organic matter content, and in it, the average total plate count was estimated at 2794 colonies/g, the average *Clostridium* count was estimated at 800 colonies/g, and the fecal contamination was not confirmed.

The ancient people used *peat extract baths*, and the antiseptic properties of *peat mud* had been recognized in World War I when it was applied to wounds to prevent infection. *Peat* has been extensively used in Europe for the last 200 years as a medicinal preparation in baths and as *mud* or *peloid packs* as to treat rheumatic diseases, gynecological disorders, osteoarthritis, lumbago, sciatica, skin diseases, and many other ailments. In Germany, peats are considered national resources. Peat pastes are semi-solid systems used in *medical* hydrology or *balneology* and cosmetic treatments based on its chemical and physicochemical properties (Dudare and Klavins 2013; and Gomes de Melo et al. 2015). Peats are complex mixtures of organic and inorganic components. Organic fraction comes from vegetable wastes transformed under anaerobic and waterlogged conditions for extended periods and includes humic acids, humin, and fulvic acids as principal constituents. Organic compounds have demonstrated biological activities, which make them potentially useful in topical health care and cosmetology (Summa and Tateo 1999; and Beer et al. 2003a, b). Peat having a high organic content must be stored in a moist state to be biologically and therapeutically active. Once peat dries, it is impossible to re-hydrate making it inert, naturally with no medicinal properties.

At last *bioglea* or *biofilm* is an *essentially organic peloid* that occurs as a layer of prokaryotic organisms (mainly bacteria) that have aggregated to form a colony for metabolic cooperation that is attached to a surface of solids (e.g., rocks), liquids (stagnant pools of water), or living tissues. *Biofilms* can be used as *natural peloids* in medical hydrology. For instance, in the Spa of Corona (Crown Spa), Caldeiras da Ribeira Grande, São Miguel island, the Azores archipelago, hot mud and biofilm are deposited in an artificial tank constructed to collect the mud produced by a nearby hot spring of the fumarolic field. Mud and biofilm, the last being fixed on the tank walls, are used in the treatment of various dermatological and osteoarticular diseases. Also, in the Beija pudles and in the outdoor swimming pool or thermal pool of the Terra Nostra Garden Hotel and Spa, structures located in the Furnas Valley, São Miguel island, the Azores, reddish-brown *biofilms* are removed from the pool's walls and directly applied to the skin in order to treat diseases such as dermatitis and fungal infections. The water of the thermal pool referred to that is located inside the Terra Nostra Park, an ex libris of the Azores created by Thomas Hickling, an American dealer who loved São Miguel island and the Furnas Valley in particular, has its source in a spring which water enriched in Fe is characterized by temperatures within the range 37–40 °C. *Biofilms* eventually can harbor human infectious (pathogenic) agents, but the microbiota from the *biofilms* of thermal pool of Terra Nostra Park.

Certain pathogenic bacteria could be present in *natural peloids* and even in *peloids s.s.* currently used as *mud packs* and *peloid packs* or *cataplasms*, and being in direct contact with the skin they are potentially more hazardous than *compresses which are currently used too*. Within bacteria *Clostridium perfringens*, *Clostridium botulinum*, *Clostridium tetani*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* are pathogenic species that could be present in both *natural peloids* and *artificial peloids*. In the last type of peloids, the microbial source could be either the mineral water (thermal or not thermal) or the clay or both.

In what clay is concerned the mostly used clays (kaolin and bentonite) in pharmaceutical formulations, the Pharmacopeias (EP fourth edition and USP 29) establish the maximum of 10^3CFU/g for microbial content.

Within the European countries, with exception of certain regions of Germany and France, there are no quality standards or guidelines for *muds* or *peloids* utilized for therapeutic purposes. In Germany, the guidelines are as follows: mesophilic heterotrophic microorganisms determined at 20 °C < 10^7 CFU (colony-forming units)/g; mesophilic heterotrophic microorganisms, 36 °C < 10^7 CFU/g; *Pseudomonas aeruginosa*, 0 CFU/g; yeasts and fungi, <10^4 CFU/g; coliforms, <10^4 CFU/g; *Escherichia coli*, <10^2 CFU/g; and *Staphylococcus aureus,* 0 CFU/g; $5.5 < \text{pH} < 9.5$.

Outside of Europe, in Cuba, a country where *healing muds* and *peloids* have a paramount importance for therapeutic and cosmetic purposes, the sanitary control of these materials has deserved high concern, reason why a regulation (Norma Cubana de Peloides, 1998) was established containing references to peloids' chemical and microbiological specifications.

In Spain, a country where *healing muds* or *natural peloids* and *peloids* are used for therapeutic applications complementary to those provided by mineral-medicinal waters inside the balnearies of thermal centers and of thalassotherapy centers too, there is no specific legislation for *healing muds* and *peloids*. These materials are considered as products derived from the mineral-medicinal waters. Hence it is understandable that the legislation applied to the use of these waters could well be applied to *healing muds* and *peloids*. As a matter of fact, this is what happens in Spain, treatments taking place in balnearies under medical supervision. Microbiological control follows the same requisites that mineral-medicinal waters do.

Compared to *natural peloids*, the *designed and engineered peloids,* which are a particular type of *manipulated and modified peloids,* could be sanitary much safer, in terms of hazardous chemicals and pathogen microorganisms, because each individual main components, mineral water and clay, could be previously analyzed, and adequate control could be carried out during each stage of the *peloid* preparation.

Manipulated and modified peloid – It is a *natural peloid* that after being extracted from the natural occurrence site had undergone manipulation and maturation inside the *spa* in previously established conditions, hoping that the eventual changes on its physical, chemical, and biochemical properties could improve the therapeutic benefits of the *manipulated and modified peloid*. The manipulation or modification process could be still more developed in case the final product, although equally based on natural components, is *designed and engineered* inside specialized manufacturing units, located indoors or outdoors the application units, i.e., the *spas*.

Mud therapy based on the use for therapeutic or skin care purposes of *mud* or *natural peloid*, maturated and applied at or near the natural site of occurrence, is progressively losing applied interest in favor of *peloid therapy* based on *manipulated* and *modified peloids*, which undergo refinement, beneficiation, modification, and maturation, in order to be used inside the *spas*, due to the following facts:

1. The access to *natural peloids* is becoming more and more difficult due to environmental restrictions, since the deposits of natural peloids are, as a rule, located inside *environmental protected areas*.
2. The geologic sites where *natural peloids* occur are *open systems highly vulnerable to anthropogenic contamination particularly due to pathogen microorganisms*; the vulnerability could be due also to potential toxic inorganic and organic compounds resulting from nearby urban, agricultural, and industrial activities; the situations referred to would make either very difficult or unfeasible the sanitary control and safety of *natural peloids*.
3. The use of *natural peloids* could be hazardous, as happens with mud deposited by acidic volcanic waters which are characterized by very low pH (2–3) naturally aggressive to the skin, and usually they show relatively high contents of *heavy metals*.
4. The complexity of *natural peloids* composition and characteristics makes difficult not only the identification of the *healing active principles* but also the understanding of the *healing mechanism of action and process* and the control of both *composition* and *sanitary state* too.

As a matter of fact, the four aforesaid facts justify the increasing interest for *peloid therapy* based on *manipulated and modified peloids* particularly on those called *designed and engineered peloids*, whose formulations could be based on a chemically and microbiologically controlled mixture of a *particular clay* preferentially with a *particular mineral water*, mixture to which *functional additives* able to provide benefits in particular health disorders can be added.

Designed and engineered peloid – It is a particular type of *manipulated and modified peloid* that can be either produced inside specialized manufacture units with the objective of its trading for application in *spas* or produced inside the *spa* facilities where it is applied. In both cases, the products could be designed and manipulated to comply with both therapeutic and cosmetic anticipated goals and functions too.

Designed and engineered peloids easily can be manufactured using, for instance, specific mixtures of one almost monomineral and commercial clay (e.g., *kaolin* or *bentonite*), preferably of pharmaceutical grade, with one specific mineral water (e.g., seawater and salt-lake water) or natural mineral water (e.g., spring thermal water). These mixtures after undergoing manipulation and maturation could be beneficiated, for instance, through the incorporation of *healing functionally active*

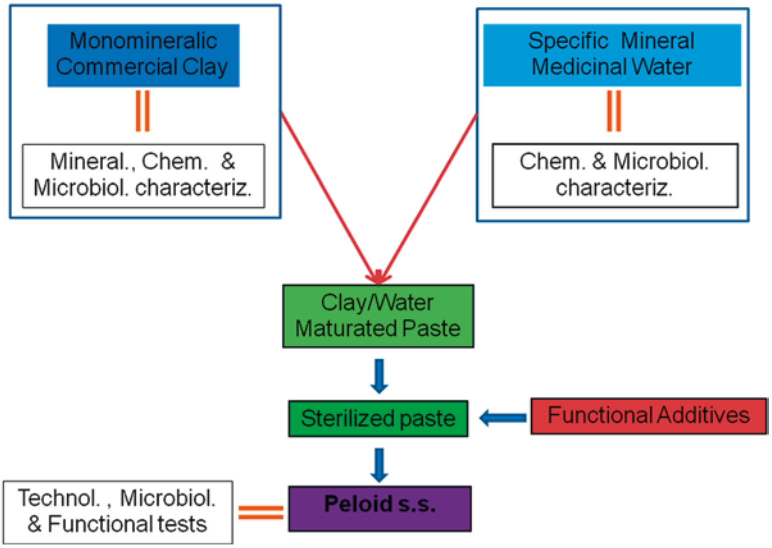


Fig. 7.5 Flow sheet of the preparation of *designed and engineered peloids* (Gomes et al. 2015)

additives, either natural (e.g., the natural polymers *chitin*, *chitosan*, *starch*, *gellan gum*, and *aloe vera*) or synthetic, characterized by analgesic, anti-inflammatory, anti-bactericidal, antioxidant, anti-cellulite, anti-psoriasis, and anti-acne properties.

Chitosan, in particular, is the second most abundant biopolymer on Earth after cellulose and widely distributed in crustaceans and insects, being extracted from crab and shrimp shells. It is a cationic natural polymer, non-toxic, biocompatible, and biodegradable, which has been a matter of much investigation and used as a topical dressing in wounds and burns owing to its hemostatic property and other properties previously referred to both as chitosan-based nanohybrid membranes and as *chitosan/montmorillonite* biocomposites (Onmainty et al. 2016; Moghadas et al. 2016; Rabea et al. 2003; and Dai et al. 2011).

Natural mineral water is defined as a bacteriologically acceptable mineral water of relatively deep circulation into the earth's crust that shows specific physical and chemical properties stable at the source or emergence. These properties may bring about therapeutic benefits or simply favorable health benefits. The emergence or source of natural mineral waters can be either natural (mineral spring) or related to a deep-seated water well. Generally, natural mineral waters used for therapeutic purposes emerge as natural thermal springs within the territories of thermal resorts.

Figure 7.5 shows the flow sheet we have adopted for the preparation of *designed and engineered peloids*. Due to their simple composition, controlled processing, and evaluation, *designed and engineered peloids* of both medical and cosmetic typologies easily can be periodically submitted to both chemical composition control comprising the identification and quantification of inorganic or mineral and of organic constituents and sanitary control comprising the identification and quantification of pathogenic microorganisms.

Table 7.2 Microbiological limits for cosmetics European Standard EN ISO 17516:2014 (Cosmetics-Microbiology-Microbiological Limits)

Types of microorganism	Products specifically intended for children under 3 years of age, the eye area or the mucous membranes	Other products
Total aerobic mesophilic microorganisms (bacteria plus yeast and mold)	$\leq 1 \times 10^2$ CFU per g or ml [a]	$\leq 1 \times 10^2$ CFU per g or ml [b]
Escherichia coli	Absence in 1 g or 1 ml	Absence in 1 g or 1 ml
Pseudomonas aeruginosa	Absence in 1 g or 1 ml	Absence in 1 g or 1 ml
Staphylococcus aureus	Absence in 1 g or 1 ml	Absence in 1 g or 1 ml
Candida albicans	Absence in 1 g or 1 ml	Absence in 1 g or 1 ml

Due to inherent variability of the plate count method, according to USP chapter 61 or EP chapter 2.6.12 (Interpretation of Results), the results are considered out of limit if:

a - > 200 CFU/g or ml

b - > 2000 CFU/g or ml

Note: When colonies of bacteria are detected on Sabouraud dextrose agar, Sabouraud dextrose agar containing antibiotics may be used

Chemical control, for example, in what heavy metals are concerned, should comply with specifications disclosed in European Pharmacopeia (2002), US Pharmacopeia (2006), and Health Canada (2009).

In Europe, the Scientific Committee on Consumer Safety (SCCS) of the European Commission has reviewed and approved at its 10TH plenary meeting of November, 12, 2012, the regulations SCCS/1501/12 for testing and safety evaluation of cosmetic substances which are compiled in the document “Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation” (8TH revision). The “Notes of Guidance” are regularly revised and updated in order to incorporate the progress of scientific knowledge, in general, and the experience gained, in particular, in the field of testing and safety evaluation of cosmetic ingredients. The last revision (9TH revision) of the “Notes of Guidance” was adopted by SCCS at the 11th plenary meeting of September 29, 2015 (SCCS/1564/15).

Table 7.2 shows the quantitative and qualitative microbiological limits for cosmetics in Europe based on the European Standard EN ISO 17516:2014 Cosmetics-Microbiology-Microbiological Limits, standard that was approved on August 9, 2014, and that at present is widely used as international standard by the cosmetics industry.

The *designed and engineered peloids* are distinguished from the hereunder referred to *extemporaneous peloids* since they require a short-term maturation not longer than 1–2 weeks, time required to get a sufficient physical, chemical, and eventual biochemical equilibrium between all the *peloid* constituents.

Extemporaneous peloid – It is a healing mud that is prepared at the local and time of use, blending one common or one special clay (kaolin or bentonite) or special algae with natural mineral water or with seawater without undergoing maturation; it is not a real *peloid s.s.* because the maturation does not occur.

Mejide et al. 2010, and Arribas et al. 2010, have studied and assessed the effects on the mechanical and functional characteristics of skin from the application of *extemporaneous peloids* based on bentonite mixed with both sulfurous thermal water and seawater, as well as the clinical effects (expressed by scaling off and inflammation) on *psoriasis*.

Paramud or **parapeloid** or **parafango** – It is a product that is the result of the intimate blend, for instance, of bentonitic or illitic clay with paraffin.

As a matter of fact, *paramud* or *parapeloid* or yet *parafango* really is not a type of *peloid*; otherwise it is a *peloid succedaneum*; it is applied either as cataplasms or as compresses and always hot (not above 50 °C) in physiotherapy.

7.3.3 Peloid Functions, Benefits, and Risks

As a rule, both *natural peloids* and *peloids s.s.* are three-phase systems consisting of one *solid phase* consisting of inorganic, organic, or mixed inorganic/organic natural materials; one *liquid phase* consisting of mineral water from thermal spring, river, lake, or sea; and one *gas phase* consisting of H_2S, CO_2, NH_4, CH_4, or Rn. Also, as a rule, and in quantitative terms, the gas phase is irrelevant, but it could be therapeutically relevant.

According to Burguera et al. 2012, and Fioravanti et al. 2013, the H_2S, either formed from organic matter decomposition, situation common in mud of salt pans, or existing in solution in sulfurous water, a chemical type quite frequent within thermal mineral waters, would act as an anti-inflammatory and antioxidant agent in human osteoarthritic articular chondrocytes. Also, according to Yamaoka et al. 2004, and Falkenback et al. 2005, radon (Rn) therapy is known to be effective against pain-related rheumatic diseases such as osteoarthritis which is commonly treated with *peloids*. Other radioactive elements have been mentioned in few peloids both related with the solid phase – natural sediment – and with the liquid phase, natural mineral water or spring water (Tateo and Summa 2007; Tateo et al. 2009; Carretero et al. 2013; Díaz Rizo et al. 2013; Cantaluppi et al. 2014; Karakaya et al. 2015; Da Silva et al. 2015; Karpińska et al. 2017; and Díaz Rizo et al. 2018). The authors point out the possibility of beneficial or harmful health effects induced by the radioactive isotopes present in the peloids.

The inorganic component is mainly composed of a fine-grained sediment called clay, itself a very complex system that consists of *clay minerals*, as a rule, two or three species, and *non-clay minerals*, as a rule, three or four species. The organic component could be more complex and is surely less studied than the inorganic component; it could contain several eventually beneficial active hydrophilic and lipophilic compounds.

Peloids are used under *medical counselling and supervision* inside the facilities of health resort medicine or spa therapy centers. The health benefits of peloids are being attributed to a combination of actions, and within these, the *thermal actions* and the *chemical actions* are currently the most emphasized.

Clinical evidence based on epidemiological studies which are reported in specialized literature emphasizes the benefits of *mud therapy* and *peloid therapy* on degenerative and inflammatory rheumatism taking advantage of peloids' analgesic, anti-inflammatory, antioxidant, and antimicrobian actions.

Several authors have emphasized the benefits of *peloid properties* and *peloid therapeutic functions*: Veniale 1996, 1997, 1999; Carretero 2002; Carretero et al. 2006, 2013; Maraver 2013; Tefner 2014; Maraver et al. 2015; Roques 2015; Fioravanti et al. 2014; Fioravanti and Chelesschi 2015; Meijide et al. 2014, 2015; and Gomes 2015. Also, there is evidence of the positive effects of *peloids* on dermatological affections, especially on psoriasis, acne, and seborrhea, as well as on skin care functions: cleansing, degreasing, exfoliating, hydrating, tonifying, and reaffirming.

Several authors have emphasized too the benefits of *peloid properties* and *peloid dermatological and aesthetic functions* in several skin affections such as acne, seborrhea, and psoriasis: Carabelli et al. 1998; Delfino et al. 2003; Argenziano et al. 2004; Dreno 2004; Amin et al. 2007; Arribas 2012; Garcia 2014; Bascini et al. 2014; Meijide et al. 2014; Garcia Matas et al. 2014; and Tejero Garcia 2014.

7.3.3.1 Examples of Peloid Benefits and Risks

Benefits

- *Rheumatologic diseases:*

Osteoarthritis (AO), back pain, and fibromyalgia.

Dermatologic diseases:

Psoriasis, acne, and seborrhea.

Risks

- *Contamination of toxic trace elements:*

Pb, Cd, Hg, Al, As, Sb, Zn, Cr, Cu, Ni, etc. could be incorporated through dermal absorption.

Contamination of microorganisms:

Pathogenic microorganisms could cause skin infection and other skin disorders; manipulation and maturation could favor the development of pathogenic microorganisms.

Microbiological study of *natural peloids* and *manipulated or modified peloids* or *peloids* comprises the determination of indicators such as:

1. *Total plate count*, number of colonies that will grow within 48 hours at the temperature of 37 °C and are determined in 1 g of healing mud/peloid.
2. *Total coliform count*, also determined in 1 g of healing mud/peloid, number that could indicate fecal contamination.

Decontamination of pathogen microorganisms could be achieved either by heating at 160 °C for at least 1 h, a process that could cause irreversible changes in the *peloid* system, or by exposure to gamma radiation (Viseras et al. 2007).

Favero et al. 2016, report an effective method for decontamination of the clay raw material (e.g., kaolin or bentonite) used in the preparation of *cosmetic peloids* which are very much demanding in sanitary terms (specifications disclosed, for instance, in United States Pharmacopeia, 2006, and in British Pharmacopeia, 2008), in case pathogen microbial contamination is found in the clay.

7.3.3.2 Mechanisms of Action of Healing Mud and Peloid

Thermotherapeutic Action

In the treatment of rheumatic diseases, particularly osteoarthritis, *healing mud* or *natural peloid* and *peloid s.s.* are currently applied directly onto the skin of the affected areas after being warmed up to 42–45 °C, for periods of normally 20–30 minutes.

Local vasodilatation and hyperemia improves:

1. Blood irrigation and circulation in the skin and underlying tissues.
2. Liberation of histamine and acetylcholine.
3. Modification of serum levels of amino acids.
4. Increase in plasma beta-endorphin demonstrated to occur has an analgesic and antispastic effect, most probably the key factor (Pastor 1998; Fioravanti et al. 2011; Fernandez-Lao et al., 2012; Sarsan et al. 2012; Maraver 2013; Tricás et al. 2014; and Tuulik et al., 2015).

Armijo et al. 2014, clearly state that there is no doubt that the main therapeutic action of the peloid's therapy depends on the thermal properties.

The thermotherapeutic action of both healing mud and peloid provided by the heat very much depends upon the thermal properties of these materials, such as:

1. *Heat capacity*, the highest possible.
2. *Specific heat*, the highest possible.
3. *Cooling rate*, the lowest possible.

All the assets of these properties depend upon the *texture*, the *nature and quantity of the solid phase*, as well as the *nature and quantity of the liquid phase* (Armijo 1991; and Armijo et al. 2016). These authors found out that for clay pastes with 60% water, the cooling rate is slower for bentonite-based peloids than for kaolin-based peloids, different behavior that in our opinion could be justified by particle size and distribution as well as by particle aggregation. Therefore, in terms of just thermotherapeutic action, *bentonite-based designed and engineered peloids* are preferred to *kaolin-based designed and engineered peloids*.

The thermophysical properties of the healing mud or peloid should be added as follows:

1. The *heat capacity* (Cp) of a substance, in this case healing mud or peloid, is defined as the thermal energy required for increasing its temperature by one degree under constant pressure conditions.
2. The *specific heat* (cp) of a substance, *healing mud* or peloid, is defined as the heat capacity per unit mass (m), expressed as cp = Cp/m.

As a rule, the *heat capacity* is expressed in J/K (Joules/Kelvin), and the *specific heat* is expressed in J/K.kg. Another important property of the healing mud or peloid is the *heat* or *thermal conductivity* (k) defined as the density of heat current per unit temperature gradient under conditions of zero electrical current and without matter mobility.

The *thermal conductivity* and the *heat capacity* are not directly related: the first is a flow of energy and the second is an amount of energy. However, there is a quantitative factor that relates these two variables, which is named *thermal retention capacity* (R) expressed by $R = Cp.\rho/k$, where ρ is the density of the *healing mud* or of the *peloid* and k is the thermal conductivity.

The *thermal retention capacity* expresses the time that takes the volume unit of the system, *healing mud* or *peloid*, to decrease its temperature by one degree when the decrease in heat per second is an amount numerically equal to the coefficient of thermal conductivity. Thus, the *thermal retention capacity* measures the heat flow of the system, *healing mud* or *peloid*, and is expressed in seconds per square meter (s/m^2).

The main factors that control the thermophysical properties of the semi-solid paste and pack are:

1. Qualitative and quantitative composition of the solid phase, generally constituted by clay minerals, non-clay minerals, and organic matter.
2. Nature and quantity of the liquid phase consisting, as a rule, of spring water or natural mineral water (thermal or non-thermal) and salt-lake seawater.

The granulometric or grain size distribution of the solid phase is another determining factor.

For similar compositions, while maintaining the nature and content of the liquid phase, the finer the grain, naturally the greater the number of contacts between grains and liquid, with consequent thermal conductivity and cooling kinetics as measured by the cooling rate which is expressed in degrees centigrade per minute (°C/minute) of the system. When applied hot, the cooling rate of the healing mud or of the peloid should be as small as possible. A certain solid phase must correspond to a certain optimum liquid phase content which must individually involve each grain and be in equilibrium with it.

Nowadays, in terms of therapeutic benefit, the cooling rate of both healing mud and peloid is a distinctive parameter, but it is not a relevant parameter. As a rule, immediately prior to topical application, the peloid is preheated to 45 °C, and the application lasts until the temperature reaches 37 °C (normal human body temperature), cooling which may take place between 10 and 20 minutes.

Assuming that the temperature of the applied mud or peloid is therapeutically a determining factor, to maintain the temperature of the applied mud or peloid, for example, at 40 °C, for longer time than normal time, such can be made overlapping both mud and peloid with a thermal mat or blanket.

Chemotherapeutic Action

Numerous studies have demonstrated that the anti-inflammatory, analgesic, chondroprotecting, and immunological actions could be attributed to the chemical properties of both *healing mud* and *peloid* (Carretero 2002; Carretero and Pozo 2007; Gomes and Silva 2007; Gomes 2013) and to the transdermal absorption of minerals (Tateo et al. 2009; Carretero et al. 2010) and organic substances (Maraver et al. 1987; Teixeira et al. 1996; Curri et al. 1997; Tolomio et al. 1999; Nissenbaum et al. 2002; Torrella 2006; Odabasi et al. 2008; Tserenpil et al. 2010; Kim et al. 2010; Suárez et al. 2011) having analgesic, anti-inflammatory, chondroprotecting, and immunological action (Roques 2004; Carretero et al. 2010; Tateo et al. 2007, 2009; Beer et al. 2003, 2013), mostly resulting from the maturation process (Galzigna et al. 1996; Galzigna et al. 1999; Veniale et al. 2004; Carretero et al. 2007; Carretero et al. 2008; Gámiz et al. 2008; Gámiz et al. 2009; Delgado et al. 2010; Fernández-González, 2010; Fernández-González et al. 2013; Fioravanti et al. 2011; and Fioravanti and Cheleschi 2015).

The organic fraction of the *healing mud* and *peloid* has been less investigated than the inorganic fraction. Indeed, there are few studies on the organic compounds and microorganisms exiting in both natural and artificial peloids, as well as on their relationships with therapeutic activity and efficacy.

In studies of *peat mud*, Beer et al. 2002, 2003, consider that the existing aqueous pharmacologically active and water-soluble (hydrophilic) substances, such as humic, fulmic, and ulmic acid derivatives, could permeate human skin in quantities sufficient to cause biologic effects.

Odabasi et al. 2007, consider that peat mud beneficial chemical effects could be attributed not only to organic hydrophilic substances but also to lipophilic low-molecular-weight substances derived from fatty acids such as palmitic acid, linoleic acid, oleic acid, stearic acid, lauric acid, and phthalic acid, and the authors have considered too that the subject requires more investigation. Also, in terms of just chemotherapeutic action, *bentonite-based designed and engineered peloids* are preferred to *kaolin-based designed and engineered peloids*, since both chemical and surface properties of smectite clay minerals, the species *montmorillonite* in particular (the basic constituent of bentonite), such as electric charge, ion exchange, and adsorption are favorable compared to the same properties of kaolinite (the basic constituent of kaolin).

The chemotherapeutic action of the *peloid* under the form of *peloid pack* is related to the flow generated between the elements and molecules (ions or polar molecules) that are either in free form present in the liquid phase of the peloid or reversibly adsorbed to the surface of the particles of both clay minerals and organic compounds constituent of the solid phase and the elements and molecules released from the part of the patient body being treated, release and intake that are induced by the fact that the temperature of the peloid is higher at body temperature.

The solid phase of the peloid, essentially constituted of clay minerals, changes the chemical composition of the liquid phase, essentially constituted of natural mineral water, spring water, or seawater.

A chemical equilibrium will be achieved in the so-called interstitial liquid that is formed and occupies the inter-particle spaces of the solid phase. Any eventual therapeutic activity of the system will mainly depend on the chemical composition of the *interstitial liquid*, the solid phase just serving as the support and vehicle for the *interstitial liquid*, making and keeping it available for interaction with the skin along the time of both healing mud and peloid application. Both inorganic and organic constituents of the interstitial liquid could permeate the human skin and eventually be responsible for the health benefits.

Clay minerals and eventually organic matter too, due to their unique cation and anion exchange properties, play a fundamental role for the achievement of that chemical equilibrium above referred to. The direction in which the elements or molecules move in said ionic flow depends on the respective concentration gradients then established. It is this transfer that can justify the said chemotherapeutic action.

In the literature, little research has been concerned with the chemistry of the healing mud/peloid interstitial liquid or fluid and with its biochemical action (Flusser et al. 2002; Codish et al. 2005; Abu-Shakra et al. 2014; Özkuk et al. 2017; Spilioti et al. 2017; Ökmen et al. 2017; Kamitsou et al. 2018; and Yücesoy et al. 2019). However, none of these authors have related the chemical nature and content of the interstitial liquid with the therapeutic and cosmetic action of both healing mud and peloid. The first three groups of researchers above referred to have studied the therapeutic activity in rheumatic disabilities – knee osteoarthritis, hand rheumatoid arthritis, and low back pain – applying mud compresses, designed and commercialized for the Ahava Company at the Dead Sea, on a group of patients and depleted mud compresses on another group of patients, the control group.

Mud compresses were composed of three layers: the innermost layer to be put in direct contact with the target joint, being wrapped in a porous fibrous cloth; the intermediate layer being an absorbent material in which the Dead Sea mud has been spread; and the external layer being a nonpermeable plastic sheath. For the preparation of depleted mud compresses, the Dead Sea raw mud underwent repeated washings with tap fresh water.

In the experiences carried out by Flusser et al. 2002, and Codish et al. 2005, post-treatment evaluation of patient group treated with mud compresses revealed significant reductions in knee pain and in the number of swollen and tender joints, respectively. Otherwise, in the post-treatment evaluation of patient control group, i.e., the group of patients treated with depleted mud compresses, no improvement of the disabilities had been revealed.

In the experiences carried out by Abu-Shakra et al. 2014, post-treatment evaluation revealed that pain severity was much reduced in the case of patient group treated with mud compresses. No pain reduction was verified in the patients of the control group treated with depleted mud compresses. Both types of compresses were warmed up before application. No fine chemical characterization of mud interstitial liquid, before and after application, was performed.

Peloids used for therapeutic purposes are currently applied as both mud packs and mud compresses. Experience as shown that the peloid action is particularly more effective in case the peloid is directly applied on the skin.

The experiences above referred to show the therapeutic relevance of the liquid phase of both healing mud and peloid, the efficacy of the skin permeability and chemical uptake being potentiated by warming up both healing mud and peloid immediately before application. More clinical studies are welcome.

The decrease in the initial temperature (45–50 °C) of the *peloid*, which in 15–20 minutes reaches the body temperature, can be canceled by applying a blanket to the *peloid* layers in order to maintain the peloid temperature for a longer period of time (recommended about 30 minutes). To overcome differences on the cooling kinetics of the *peloid* system, it is recommended to cover the *peloid* pack with a small and flexible electric mat, easily found in the market, to keep constant and controllable the *peloid* pack temperature, not higher than 45 °C, for the recommended time.

Biological and Biochemical Action

Recent studies indicate that the healing properties for skin diseases of clay-based *healing mud/peloid* could be attributed to their microbial composition and activity (Falkinham et al. 2009; and Sharma et al. 2018). According to Sharma et al. 2018, till date there have been a very few studies on the microbial diversity of natural healing clays. Hence, determining and characterizing the native microbial composition is mandatory to decipher the role microbes play in healing various skin diseases.

Previous studies have demonstrated the role of clay microbes in skin healing (Nissenbaum et al. 2002; Falkinham et al. 2009; Pesciaroli et al. 2016; and Svensson et al. 2017).

Several recent studies had validated the role of microbes in perpetuating skin's physical and immune barrier under healthy and/or stress conditions (Belkaide and Segre 2014; and Ganju et al. 2016), and other studies have reported the beneficial effect of pre- and probiotics on skin health, maintenance, recovery, and skin disease treatment (Al-Ghazzewi and Tester 2014; Roudsari et al. 2015; and Jeong et al. 2016).

Many topical ointments containing prebiotics, probiotics, or bacterial cell lysates show verifiable skin benefits (Farris 2016). Grewal et al. 2014, report one study of the use of clay/water paste from the holy shrine Chamliyal, located at the Indo-Pak border in the Samba district of Jammu region of Jamur and Kashmir, India, as an ointment to treat different skin diseases, psoriasis in particular.

Sharma et al. 2018, have analyzed the microbial phylogeny and diversity of the Chamliyal' healing clay by the analysis of whole metagenome and found out the dominance in the clay of the orders *Enterobacteriales*, *Pseudomonadales*, *Rhizobiales*, *Burkholderiales*, and *Myxococcales*.

Actinobacteria is reported to be the most dominant and diverse phylum in healthy human skin (Grice et al. 2009) and is a major group of antibiotic-producing bacteria present in the Chamliyal' clay. In the skin of healthy individuals, the abundance of *Actinobacteria* is higher than in the skin of psoriatic patients (Gao et al. 2008; Cho et al. 2012; and Fahlen et al. 2012).

There is sufficient clinical evidence from specialized literature confirming, at least, the short-term benefits of peloids which are being attributed to the combination of the factors earlier discussed. Whereas both thermal and chemical factors are considered the most effective ones, while the first is generally well established and attributed to the solid phase – clay – there is little evidence relative to the second factor, although one might expect that minerals and organic substances dissolved in the liquid phase, mineral water, of the *peloid* could interact and provide dermal absorption during the *peloid* application.

On the one hand, the solid phase of the *peloid paste* favors the maintenance of the *peloid* heat along the *peloid* application as well as the contact and eventual dermal absorption of chemical elements and molecules reversibly fixed at clay minerals' surfaces by ion exchange. On the other hand, minerals and organic substances dissolved in the liquid phase of the *healing mud/peloid paste* become able for dermal absorption along all time (around 20 minutes) of *healing mud/peloid* application. The fundamental role of the liquid phase is assumed when in health resort medicine the thermal water is considered an effective medicine. However, the hydrophobicity of the skin barrier formed by the epidermis *stratum corneum* (*SC*) layer does not facilitate the percutaneous penetration of hydrophilic substances, minerals, and polar organic compounds (Gomes 2015).

Mineral salts, trace elements, and organic polar compounds carried in solution in the hydrophilic mineral water cannot easily penetrate the skin (Bolzinger et al. 2012).

Very recently Morer et al. 2017, carried out a comprehensive literature review on balneotherapy looking at evidences about the specific therapeutic role of mineral elements and other chemical compounds present both in mineral waters and in the liquid phase of the *peloid* bearing such mineral waters.

The authors have yet discussed the study methods used to evaluate the therapeutic role referred to. For this purpose, they had selected the double-blind randomized clinical trials that have been used to assess the effects of treatments based just on mineral water or on *peloid*-bearing mineral water (patients of the "mineral group") compared to patients treated with tap water or with *healing mud/peloid*, both without specific minerals or chemical compounds (patients of the "non-mineral group").

A total of 1118 patients suffering from rheumatological and musculoskeletal diseases (chronic low back pain, knee osteoarthritis, hand osteoarthritis, osteoarthritis) were evaluated in the author's studies. Patients of the experimental group were treated with mineral water baths and with mineral water-bearing *peloid*, whereas patients of the control group were treated with tap water baths and with "non-mineral water"-bearing *peloid*. The authors yet found out that patients of the experimental group had better and longer improvement in pain, function, quality of life, and clinical parameters compared to patients of the control group. Notwithstanding the authors recommend well-designed studies in larger patient's populations since the existing research is not sufficiently strong to draw firm conclusions.

Forestier et al. 2016, recently have produced a systematic review of the health benefits of spa therapy on knee *osteoarthritis* (OA), and they found that crenobalneotherapy is commonly used to treat OA but evidence from previous reviewers was no sufficient. The "bioregulatory effect of balneotherapy" has been proposed as a mechanism that contributes for anti-inflammatory responses in which regulatory T cells seem to have a crucial role.

Osteoarthritis (OA) is one of the most common chronic health conditions and the most prevalent arthritic disease, generally affecting in elderly people, the synovial joints leading to cartilage destruction. OA is a public health disease that will probably increase in the future with the aging of the population (Glyn-Jones et al. 2015; and Musumeci et al. 2015).

Gálvez et al. 2019, state that besides cartilage destruction, deterioration of the bone and inflammation of the synovium cause stiffness, swelling of the joint, and consequently pain and mobility impairment. The authors based on experimental work analyzed how balneotherapy, involving the use of peloids, affects the inflammatory responses, constituting an immunophysiological mechanism underlying the proven clinical benefits of this intervention.

Pelotherapy and *mud therapy* are balneotherapy modalities, effective, well-tolerated, non-invasive, and complementary strategies in the treatment of OA (Fioravanti et al. 2012; Espejo-Antúnez et al. 2013; Liu et al. 2013; Forestier et al. 2016; Varga 2016; Antonelli et al. 2018; and Fraioli et al. 2018).

According to Varga 2016, the therapeutic activity of natural resources such as mineral water and peloids is linked with the inorganic content of water, brines, and peloids. However, the author assumes that many experimental balneological studies were not designed properly, and they needed more treated groups, including negative controls.

The experimental work carried out by Gálvez et al. 2019, shows that mud therapy affects several immune, inflammatory, and stress mediators in elderly OA patients and that the long-term efficacy of the biological effects should be investigated together with the role of temperature and physicochemical and biological composition of waters and *healing muds/peloids* in the mechanism of action of these therapies, in order to understand the effective clinical benefits.

Recent and very interesting research is looking at transdermal delivery systems attractive for both topical and systemic therapeutics. The so-called skin permeation enhancers (such as surfactants, natural oils, hydrocarbons, fatty acids, etc.) which are being looked at by several researchers such as Naik et al. 1995; Tanojo et al. 1999; Lim et al. 2014; and Pandey et al. 2014, can improve the penetration into the skin of bioessential substances by perturbing the barrier function of the *stratum corneum*.

To favor skin permeation, immediately before the *peloid* application, skin cleansing, gumming exfoliation, and hydration are recommended. According to Araújo et al. 2015, to overcome such hindrance, the cosmeceutical/cosmetics industry is innovating and developing studies involving nanobiotechnology to create and encapsulate effective functional molecules in nanocarrier systems, namely, liposomes, polymeric and solid lipid nanoparticles, and nanoemulsions, which are considered fundamental to increase the skin permeation/penetration to minerals and organics carried in solution in mineral water. However, the *peloid solid substances* can modify the properties of the liquid phase through the passage into solution of the water-soluble compounds existing in those substances and of the reversibly fixed chemical elements existing at the surfaces of the fine-grained particles of both clay minerals and organic matter.

The simple composition and easy manipulation of *designed and engineered peloids* and the easy incorporation into their formulations of amphiphilic organic compounds (containing polar water-soluble chemical groups and water-insoluble chemical groups) could overcome such hindrance.

Final Note

Very recently Carretero (2020 a, b) has reviewed all the available research information on the role played by *Clays in Pelotherapy*, information that contemplates: clay-based peloids; definition, classification, and the overall relevant mineralogical, chemical, physical, physicochemical, and organic composition and properties of peloids; and medical applications of peloids. The outcome of such excellent survey involving more than 300 publications points out that the therapeutic efficacy of peloids by means of in vitro and in vivo studies, or by means of clinical trials or studies, demonstrated that *peloids* can improve the ailments of some diseases, but in no case the *peloids*' composition and properties were related to their therapeutic activity and efficacy. Hence, combined studies are required.

7.3.4 Databases of Publications on Medical and Cosmetic Pelotherapy

A significant number of publications on medical and cosmetic pelotherapy as well as their quality appraisal can be found on the following databases: MEDLINE (PubMed), EMBASE, The Cochrane Library (Cochrane database of systematic reviews and clinical trials), DARE (Database of Abstract Reviews of Effects), and HTA (Health Technology Assessment).

Maraver 2017, has investigated the actual situation, based on the number and category of the scientific papers published during the last 4 years, of the effects of therapeutic peloids on the human body (identification of both controlled and randomized clinical studies), using the database PubMed®/MEDLINE (Mud Therapy), and concluded that the actual medical research on *pelotherapy* is more active as ever.

The author has selected 20 (twenty) articles produced in 6 (six) countries: Spain (2), Hungary (2), Israel (1), Italy (11), Tunisia (1), and Turkey (3). Most of the articles (12) were dedicated to knee osteoarthrosis. Also, during the same period of time, 10 (ten) systematic reviews on medical pelotherapy, 4 (four with meta-analysis), have been produced in 8 (eight) countries: Germany (1), China (2), Spain (1), France (1), Holland (1), Italy (2), Japan (1), and Portugal (1).

Gómez et al. 2019, report the scientific output of five *Iberoamerican Congress of Peloids* which have been held in Baiona 2007, Lanjarón 2010, Azores 2013, Caldes de Boí 2015, and El Raposo 2017. In 2019 the VI Congress was held in Termas de Copahue, Neuquen, Argentine, and in 2021 the VII Congress will be held in Colombia.

Fundamental and applied studies on *peloids* and naturally on *mineral waters* used in health resort medicine spas are targets of international organizations, such as FEMTEC, IMHG, and ESPA.

FEMTEC, the World Federation of Hydrotherapy and Climatotherapy, founded in 1937 gathers the public and private institutions that represent the thermal establishments in the respective countries. At present, it has more than 30 member countries (either statutory or affiliated). FEMTEC, based in Italy, is the only non-governmental organization (NGO) in the sector entertaining official relations (accreditation) with the World Health Organization (WHO). FEMTEC regularly organizes Scientific Congress; the last one the 72nd Congress was held in Halkidiki, Greece, in Oct. 2019.

IMHC, the International Society of Medical Hydrology and Climatology, organizes Scientific Congresses; the last one the 44th Congress was held in 2019, in Wieliczka, Poland, and the 45th Congress will take place in 2020, in Dax, France.

ESPA, the European Spas Association, is an umbrella industry organization representing 20 European countries, whose objective is to promote spas and balneology in Europe and to take care that the natural remedies based on mineral water, landscape, and climate are available to a great number of citizens and visitors as possible.

7.4 Clay Minerals in Biocomposites and in Controlled Delivery Systems for Medical and Pharmaceutical Applications

7.4.1 Clay Minerals in Biocomposites

Biocomposites are materials composed of biomolecules and inorganic solids, such as clay minerals. Very recently Oliveira et al. 2018, produced an interesting article on “Immobilization of biomolecules on natural clay minerals for medical applications.” These authors consider biomolecules a group of organic entities of biological origin, such as polysaccharides, lipids, vitamins, enzymes, amino acids, peptides, proteins, and nucleic acids. However, systems containing biomolecules often show restricted recovery and reuse because of their lack of stability at elevated temperature, in organic solvents, and in a gastrointestinal environment (An et al. 2015).

Hybrids organic-inorganic, for instance, biomolecule-clay mineral, can protect biomolecules from degradation (Tully et al. 2016).

Clay mineral surfaces through their electrically charged sites can react and interact with the biomolecules, situation that can explain the interest of nanocomposites based on clay minerals-biomolecules for biomedical and pharmaceutical applications, e.g., drug carriers for delivery systems, wound healing, biosensors, and scaffolds. Indeed, clay minerals combining its nanometric particle size with their adsorptive capacity, lack of toxicity, and biocompatibility are really promising materials to be used as biocomposites able to immobilize biomolecules on their electrically charged surfaces, characterized for having positive and negative sites, and as so high surface reactivity (Ruiz-Hitsky et al. 2015).

Clay minerals can reversibly fix and protect the biomolecules, organic entities of biological origin, such as polysaccharides, lipids, enzymes, amino acids, peptides, and nucleic acids.

According to Jayrajsinh et al. 2017, the interaction between nanoclays and organic compounds has been studied in different areas of research, such as engineered nanomaterials for medical and pharmaceutical applications.

7.4.2 Clay Minerals as Drug Delivery Systems

Clay minerals due to unique properties, nanometric size, varied crystal shape, high retention capacity, varied rheology, and non-toxicity, have been used widely as carriers for efficient controlled delivery of drugs by modifying their release (rate and/or time), increasing the drug stability, improving the dissolution profile of a drug, or enhancing their intestinal permeability (Viseras et al. 2019).

Massaro et al. 2018, present a summary of the advances in the use of clay minerals in the pharmaceutical field, focusing on kaolinite, montmorillonite, sepiolite, and halloysite. Also, the authors discuss the clay mineral properties, their application as sustainable drug carriers and releasers of biological active species, and their functionalization. The functionalization of clay surfaces, by means of supramolecular interactions or covalent modifications, opens different ways to obtain interesting nanomaterials which show improved biological properties with respect to the unmodified ones.

As a matter of fact, the required clay minerals can undergo some modifications in order to improve their natural properties. For instance, in the case of montmorillonite, the relatively easy manipulation in terms of dispersion and swelling of their particles could allow rheology control, stability, gelification, and dispersion. Even synthetic clay minerals can be produced for specific applications, as is the case of *synthetic smectites*, that offer the possibility to optimize the conditions for the incorporation of model drugs, because this way the interference of spurious phases in the interpretation of the results is avoided (Hernández et al. 2018).

Within the clay minerals, those belonging to the smectite group and to the kaolin group are the most interesting as drug carriers. Due to the small particle size and tubular shape with an empty lumen, halloysite, $Al_2Si_2O_5(OH)_4\ nH_2O$, may be used to encapsulate active agents that can benefit medical and chemical applications.

The small tube size makes halloysite suitable for applications in bio-CPN (bio-clay-polymer nanocomposite) and tissue engineering, whereas the tube lumen can incorporate and immobilize biomolecules like enzymes and proteins (Abdullayev and Lvov 2016).

The numerous research-involving halloysite applications have been particularly focused on halloysite utilization as controlled-release nanocontainer, which are interesting in bionanocomposites, drug delivery, and protective coatings.

7.4.2.1 Halloysite Nanotubes as Unique Drug Delivery Systems

The use of *halloysite nanotubes* to transport and release certain drugs in a controlled manner was first used by Price et al. 2001. In addition, *halloysite nanotubes* are inert and stable in the pH range (3–10) (Lvov et al. 2016), and "in vitro" studies of biological tissues and cells have shown that they are biocompatible.

Lvov et al. 2016; Vergaro et al. 2010; Fakhrullin and Lvov 2016; Fakhrullina et al. 2015; and Massaro et al. 2017, showed that the use of *halloysite nanotubes* is safe (without cytotoxicity) when added to cell cultures in concentrations up to 0.2 mg/mL. Also, recently Hanif et al. 2016, present a very interesting review of the application of *allophane nanotubes* as new drug delivery systems.

Halloysite nanotubes 50 ± 10 nm in diameter and 15 ± 5 nm lumen have been used in the loading and encapsulation of certain drugs and in the conditioning of their release. The loading can be optimized by varying the pH and the alcohol/water ratio in the solvent.

Figure 7.6a, b show an image TEM of halloysite nanotubes and an orthogonal section of one halloysite nanotube, respectively.

Recent studies of *halloysite nanotubes* show their potential as cheap, readily available, safe, and biocompatible nanomaterials and have also shown that organic/inorganic composites of *allophane nanotubes* have advantages over carbon nanotubes or metal oxides, being able to store and release in a controllable way functional agents such as antioxidants, drugs, or proteins, providing possibilities in the fields of drug delivery, antimicrobial materials, self-curative composites, and also regenerative medicine. However, the problem remains that *halloysite nanotubes* are not biodegradable because there are no biological mechanisms that lead to their degradation inside the human body. They also cannot be injected intravenously. But the field of external medical treatments based on controlled and sustained release of encapsulated drugs is strongly promising.

Hári et al. 2016, have published an interesting article on the adsorption of a particular active molecule on the surface of *halloysite* tubes for its controlled release as drug delivery.

Pierchala et al. 2018, have shown the potential of *multilayered polylactic acid/halloysite* membranes to be used in the prevention of infection in bone regeneration applications, since they allow the slow drug release of the specific antibiotic

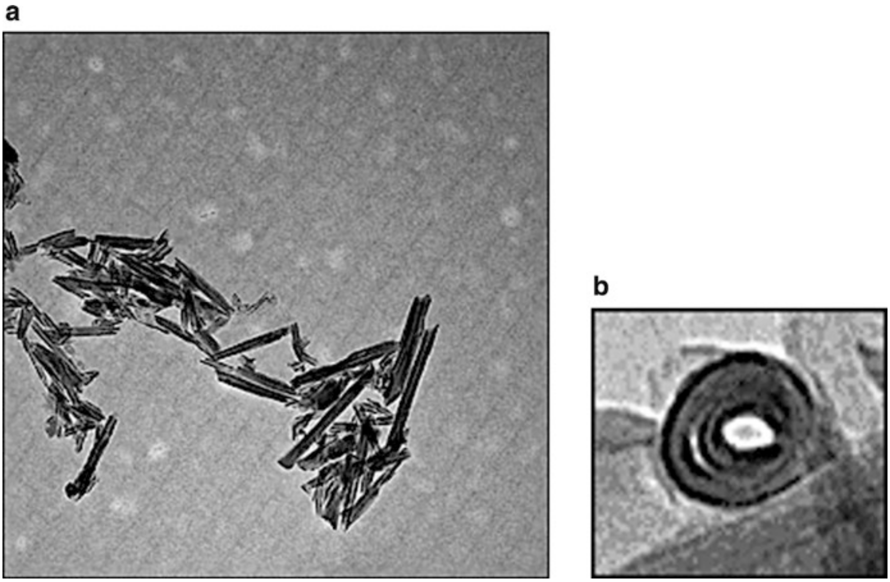


Fig. 7.6a (**a**) Image TEM of *halloysite* nanotubes. (**b**) Orthogonal section of a *halloysite* nanotube (*In:* Lvov and Price 2015)

aminoglycoside (*gentamicin*) which antimicrobial efficacy was tested on gram-positive (*Staphylococcus aureus*) and on gram-negative (*Escherichia coli*) bacteria.

Aguzzi et al. 2016, present a review of possible applications of *allophane* in nanodrugs, i.e., the use of nanotechnology in drugs.

Nanorolls or nanotubes can be produced from lamellar *kaolinite* which is much more frequent in the natural environment than *halloysite* using complementary application technological processes called intercalation and exfoliation (Detellier and Schoonheydt 2014). Bionanocomposites based on *kaolin/polymer* can be produced (Letaief and Detellier 2013).

Wilson and Keeling 2016 report tubular *halloysite* deposits at the global level, the geology of these deposits, and the physical characteristics of the mineral.

7.5 Microbicidal Clay or "Killer Clay"

7.5.1 Background Data

Antimicrobial materials have the ability of inhibiting the growth or even *killing certain types of microorganisms. The search for products having* antimicrobial properties has gained particular importance in various applications, such as in raw materials for cosmetics and pharmaceuticals, *hospital and veterinary products*, and *food manufacture and animal feeding*, *among* others.

Microbial infection has been a constant presence throughout human history. Former human societies have used some natural compounds (e.g., extracts of garlic) to heal health conditions actually recognized as being microbial infections. Within other natural antimicrobial agents, essential oils derived from plants, enzymes obtained from animal sources, and organic acids (e.g., sorbic, propionic, and citric) deserve to be enhanced. In the case of essential oils, their activity could be attributed to the presence of hydrophilic functional groups, such as hydroxyl groups of phenolic components and/or lipophilicity of some components. Usually, the compounds with phenolic groups as oils of clove, oregano, rosemary, and vanillin are the most effective (Lucera et al. 2012).

Since the beginning of the present century, experience has shown that some types of clay exhibit either bacteriostatic or bactericidal activity. Such action had raise high expectations when both public health and science are becoming more and more apprehensive and engaged relative to the increasing resistance of bacteria to antibiotics which are traditionally organic molecules, such as tetracycline and minocycline, which inhibit the replication of bacteria DNA, of both gram-positive and gram-negative bacteria.

Clays are one of the oldest natural earth materials used by man for healing purposes in traditional medicine, and they continue to be applied in modern life for the treatment of various topical and internal ailments (Carretero 2002; Carretero et al. 2006, 2013; Veniale et al. 2007; Ferrell 2008; Rautureau et al. 2010, 2017; Gomes et al. 2013; Williams and Hillier 2014; and Gomes 2018).

The first reports describing the antibacterial activity of some natural clay were due to Brunet de Courssou 2002; Wilson 2003; Williams et al. 2004; Hu et al. 2005; and Tong et al. 2005.

Clay bactericidal character does not exist if clay is in the dry state; only when clay is in the hydrated state, for instance, in the paste state, microbicide action exists. Such microbicide action creates high expectations when both public health and science are becoming more and more apprehensive and engaged relatively the increasing resistance of bacteria to antibiotics.

Specific clays and clay minerals have proved to be valuable in the treatment of bacterial diseases, including infections for which there are no effective antibiotics such as *Buruli ulcer* disease caused by *Mycobacterium ulcerans* and multi-drug-resistant infections.

The first indications of the bactericidal character of certain clays arose when the French humanitarian and philanthropist Line Brunet de Courssou who ran a clinic in the Ivory Coast found that a certain type of clay of the so-called French green clay type from his native country. Such type of clay being supplied by the French enterprises Argicur and Argiletz was very effective in combating *Buruli ulcer* that is a very common infectious disease in tropical regions – caused by the bacterium *Mycobacterium ulcerans* expressed by the so-called flesh eating, i.e., the necrosis of the skin tissues of both arms and legs. *Mycobacterium ulcerans* produces a lipid toxin, *mycolactone*, which destroys the fatty tissues under the skin (George et al. 1998, 2002).

The healing capacities of two apparently similar "French green clay," with references CsAr02 and CsAg02, had been assessed, but only the extended application of the clay CsAg02 caused tissue regeneration and wound healing. The observations of Brunet de Courssou could be validated by Williams et al. 2004, and Haydel et al. 2008.

Mycobacterium ulcerans is the third most common mycobacterial infection after tuberculosis and leprosy (Sizaire et al. 2006). The bacterium had been isolated by MacCallum in the Bairnsdale region of Australia. The disease, first described by Albert Cook in *Buruli* ´s patients, in Uganda, causing skin loss and, of course, deformities and disabilities, was endemic in countries of Central and West Africa.

Earlier in France, Brunet de Courssou had the experience of the successful use of green clay, mainly used in pelotherapy, in the treatment of wounds and insect bites, applied topically in paste form after being mixed with water. Hence, Brunet de Courssou had imported the same type of clay for use in the Ivory Coast clinic. Brunet de Courssou, in 2002, used the mixture of the two clays, "iron-rich illite-smectite clays" known as "French green clays" with water and margarine; the mixture under the form of paste was applied topically to patients, approximately 50; and he documented the benefits verified. The clay paste applied onto the ulcerated sites was removed, the wound cleansed, and the application renewed at least once daily.

The results were presented to a panel of *Buruli ulcer* specialists at the World Health Organization in 2002. Experts, while impressed with the results achieved, decided to require research that would justify the curative effects of clay before funding was provided to Brunet de Courssou for further research. In the meantime, Brunet de Courssou dies, but her son Thierry has taken on the interesting cause of his mother and, as such, the need for investigations. Thierry applied for help to the Clay Mineral Society, having competed with the geochemistry Lynda Williams of Arizona State University for the planning and execution of the investigations. For this purpose, Lynda Williams counted with the contribution of the microbiologist Shelley Haydel of the same institution.

The bactericidal abilities of the above two clays were tested against five bacterial species, *Mycobacterium marinum* (very similar to *Mycobacterium ulcerans*), and antibiotic-resistant *Staphylococcus aureus* strains. The behavior of the two clays was different: one showed no effect on the bacteria and, in some trials, even promoted its growth; the other completely inhibited the growth of bacteria and, to a significant extent, reduced the number of bacterial cells in cultural tests, their action behaving like the action of a broad-spectrum antibiotic. The investigations continued to involve other scientists besides Lynda Williams and Shelley Haydel and the results were published.

Williams et al. 2008, reported the results of detailed studies on the mineralogy and geochemistry of the two aforesaid clays in order to determine the factors justifying their curative abilities when applied topically as poultices to patients infected with *Mycobacterium ulcerans*. Although more research was considered necessary, for the authors, the mechanism of bactericidal action of one of the clays would not be physical (because the clay did not penetrate the cells of the bacteria) but rather chemical (the pH and the oxidation state of the solution surrounding the nanometric clay particles would generate conditions that inhibit the viability of pathogenic bacteria). Also, Haydel et al. 2008, reported the results of the tests performed on the evaluation of the bactericidal action of two iron-rich French clays used by Brunet de Courssou in the treatment of *Buruli ulcer* patients on various gram-negative and gram-positive bacteria and, of course, on mycobacteria.

It has been demonstrated that the specific clay with reference CsAg02 had bactericidal activity against pathogenic *E. coli*, extended-spectrum β-lactamase (ESBL) *E. coli*, *Pseudomonas aeruginosa*, *Mycobacterium marinum*, and a combined bacteriostatic/bactericidal effect against *S. aureus*, penicillin-resistant *S. aureus* (PRSA), methicillin-resistant *S. aureus*, and *Mycobacterium smegmatis*. However, it has been demonstrated too that other clay with reference CsAr02 having chemical and physical properties similar to those exhibited by CsAg02 is characterized by either less anti-bactericidal activity or just bacteriostatic activity, relative to the same strains. The authors had also showed that relevant changes in clay mineral structures due to dehydration and at least partial dehydroxylation caused by heating at 550 °C do not affect both antibacterial and bacteriostatic activities.

Mineralogically identical clays can exhibit chemical variability which correlates with variability in antibacterial activity. As a matter of fact, clay chemical composition appears to be more bactericidal effective than clay mineralogical composition. Also, acidic pH favors the clay bactericidal activity. The bioavailability of metals to bacteria depends on the aqueous metal speciation in the clay poultice. The pH and oxidation state of the water added to the clay to make a poultice are important factors but not alone of the bactericidal action.

Williams et al. 2011, studied clays from deposits in other countries and concluded that the bactericidal character always relied on clays derived from the hydrothermal alteration of volcaniclastic materials or rather pyroclastic ones, as was the case in Grants Pass, Oregon, of clay “Oregon blue clay” in which illite-smectite 49.6% wt and chlorite 3.1% were the dominant clay minerals and pyrite 8.2% was the main non-clay mineral present. And, the bactericidal effect never happened when the clay appeared in the dry state.

The geochemical and microbiological studies being carried out on the “Oregon blue clay” have shown its amazing bactericide efficacy when hydrated and incubated with bacteria providing the total elimination of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and antibiotic-resistant extended-spectrum beta lactamase (ESBL) *E. coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) within 24 hours.

According to Williams et al. 2011, the investigations carried out suggest that the results obtained are due to chemical reactions enabling the disruption of a certain physiological function of the bacteria and that the clays considered bactericidal have in common the following properties, to which supplementary data provided by other authors is added:

1. Green or blue color is common to all bactericidal natural clays.
2. Bacterial natural clays are, as a rule, of volcanogenic hydrothermal origin; but the bactericidal character of *blue/green clays* of other origins had already been identified (Londono and Williams 2016; Londono et al. 2017).

3. Bactericidal natural clays contain nanocrystals (<200 nm) of the clay mineral groups illite and smectite able to provide high surface area and availability of reactive surfaces for biogeochemical interactions.
4. Ferrous iron (Fe^{2+}) and other transition metals, Cu^{2+}, Co^{2+}, Zn^{2+}, and Ni^{2+}, are present in all bactericidal natural clays.
5. Bactericidal clays are soluble under extreme conditions of pH (<4 or > 10) so that in low oxidation environments many metals are soluble and the oxidation of the transition metals increases the Eh of the suspension or pulp to values>400 mV, such as leading to the oxidation of bacteria; for pH values close to neutrality, ferrous iron and potentially toxic metals are not soluble (Williams et al. 2008; Williams et al. 2011; Morrison et al. 2016); however, for Wang et al. 2017, clay bactericidal activity could be achieved at near neutral pH = 6.
6. Soluble Fe^{2+} is a critical antibacterial agent in natural bactericidal clays (Williams et al. 2011; Morrison et al. 2016).
7. The bactericidal clays do not show attractiveness to the bacteria, and in dry environment there is no antibacterial effect; thus, the bactericidal mechanism involves components of the solution and chemical reactions that affect cell membranes or metabolic functions;
8. Clay leachate is more antibacterial effective than moist clay; initially clay leachate is antibacterial, but it loses its effect as oxidation affects the solution; the transition metals result either from the solubility of the clay or from the solubility of minerals associated therewith, for example, *iron sulfides*, as in the case of *pyrite*, FeS_2.
9. Clay serves to keep the system moist, the water being essential to keep in solution the potentially active reducing agent in order to provide its bioavailability and bioreactivity.
10. Previous clay autoclaving, even clay mineral dehydroxylation at high temperature by heating at 550 °C, does not affect antibacterial activity (Haydel et al. 2008), indicating that organic matter and hydroxyls are not associated with antibacterial activity.

Smectitic clays rich in *montmorillonite* are the most used in the preparation of antibacterial materials due to the unique and relevant properties of this clay mineral: nanometric particle size, high specific surface area (both external and internal), high sorptive capacity, negative surface electric charge, high cation exchange capacity (of both inorganic and organic cations), catalytic activity, and low or null toxicity. Also, to certain metallic elements such as silver, zinc, copper, lead, cadmium, tin, and chromium associated with clay minerals have been recognized antibacterial properties. Gaskel et al. 2012, have found the bactericidal activity of copper and zinc in cation-exchanged *laponite*. Previously the bactericidal properties of some heavy metals had been recognized too by Hassen et al. 1998, and Lansdown 2006. The same happens with alkylammonium cations, especially those of quaternary amines, used as both skin antiseptics and disinfectants. Complexes metal-montmorillonite and alkylammonium-montmorillonite can easily be performed, and few examples of such compositions are reported in the literature showing antibacterial properties.

Ye et al. 2003; Tong et al. 2005; and Hu and Xia 2006, have tested with success the antibacterial effects of the Cu (II)-exchanged *montmorillonite* on *Escherichia coli* K88 and *Salmonella choleraesuis*. Also, Morones et al. 2005, have shown the bactericidal effect of silver (Ag) nanoparticles. It is acknowledged that pollution and contamination by microorganisms can be interrupted and eliminated using certain organic and inorganic chemicals agents and certain physical agents too (heat, UV light, ionized radiations).

Within the inorganic bacteriostatic and bactericidal agents, some deserve particular emphasis: certain metals/ions such as Ag, Cu, Zn, and Au; certain metal oxides such as TiO_2, ZnO, CuO, FeO, and MgO; and certain clays. These substances can inhibit microorganism growth acting as *bacteriostatic* agents or by disrupting bacteria cell membrane can act as *bactericidal* agents. Espirito Santo (2011) proved bacterial killing by dry metallic Cu surfaces, and for David (2012), the metal Zn is bad for bacteria.

Magaña et al. 2008, have demonstrated the antibacterial activity against *E. coli* of *montmorillonite* modified or loaded with Ag^+ by ion exchange. Metallic ion exchange *montmorillonite*, as is the case of *Ag^+-montmorillonite*, dispersed in water can attract and adsorb the negatively charged bacteria, hence facilitating and promoting the antibacterial activity.

According to Williams et al. 2011, experiments were performed involving the addition to *Escherichia coli* cultures of the aqueous leachate of the bactericidal clay to which the surface fixed metals were extracted using an EDTA-oxalate solution.

Chemical analyses of the *E. coli* population killed with aqueous leachate were compared with chemical analyses of *E. coli* from the control population, with the results showing that intracellular Fe and P concentrations are higher than in the control population. The incorporation of P by the cells of the bacterium supports the idea of the regulatory role of polyphosphate or phospholipids in the control of Fe^{2+}.

The products of the Fenton reaction can cause degradation of critical cell components, but it has been deduced that extracellular processes do not cause cells to die. On the contrary, Fe^{2+} overcomes the regulatory proteins on the outside of the membranes and, being oxidized as soon as it enters the cells, precipitates as Fe^{3+}, producing lethal OH^- radicals. This interpretation explains the bactericidal action of the Fe^{2+}-bearing clay.

Cunningham et al. 2010, Otto and Haydel 2013a, b, and Otto et al. 2014, had demonstrated that the primary in vitro antibacterial mechanism of action of clays is much dependent upon soluble metal ions, which are desorbed from the surfaces of clay mineral particles when hydrated. Cunningham et al. 2010, state that the efficacy of the antibacterial activity depends much on the low pH environment required for metal ion speciation and bioavailability. Hence, the antibacterial activity of the used clay-based products may be infeasible in topical applications because they can cause damage to tissues, since the pH of the treated tissues is significantly higher than the pH of the clay-based paste or clay-based suspension. Such conditions justify the reason why the authors propose in vivo studies.

Parolo et al. 2011, showed that samples of silver (Ag^+) and quaternary ammonium surfactant-modified montmorillonite used as skin antiseptics and disinfectants exhibit suitable inhibition properties over *E. coli* growth, whereas samples of natural montmorillonite do not exhibit antibacterial activity.

Otto and Haydel 2013, in a research article entitled "Exchangeable ions are responsible for the in vitro antibacterial properties of natural clay mixtures," have identified a natural clay within four studied samples collected in the same geologic site that exhibits in vitro antibacterial activity against a broad spectrum of bacterial pathogens, in particular *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA).

Irregularly interstratified illite-montmorillonite, *montmorillonite*, and *kaolinite* were the clay mineral species identified, as well as the metals Fe, Co, Cu, Ni, and Zn, both in the raw clay and in its clay/water leachate. In the leachates, these metals that were fixed on clay mineral surfaces would be released and acting as microbicides. Also, their concentrations could be supplemented with chloride salts of Fe, Co, Cu, Ni, and Zn. The authors have analyzed the leachates or extracts of aqueous clay mixtures obtained in pH acidic conditions and found out that the concentration of metals (Fe^{2+}, Cu^{2+}, and Zn^{2+}) in solution was mainly responsible for the bactericidal activity favored by low pH (3–4.5) and that the killing activity could not be solely attributed to pH.

Morrison et al. 2013, have studied in the "Oregon blue clay" the mineralogical variables that control the antibacterial activity in the case of pathogens *Escherichia coli* and *Staphylococcus epidermidis* after being incubated with clays collected either in both reduced and oxidized zones of the hydrothermal deposit. Based on X-ray diffraction and elemental analyses, the authors found out that only the clay samples from the reduced zones (blue zones), particularly in sites where *mixed-layered illite-smectite* (sometimes called *rectorite* in case of regular interstratification) and pyrite exist, could exhibit bactericidal character. Clay samples from the oxidized zones (red or yellow zones) don't show bactericidal activity. However, the clay samples from white zones and without pyrite show bactericidal activity, although not so effective compared to the situation when pyrite is associated with clay. Using yet the technique transmission electron microscopy (TEM), the authors could follow the behavior of the bacteria cell along the incubation process, and no indication of cell lysis could be observed. The experimental work being carried out indicates that antibacterial effectiveness correlates with elevated concentrations of Fe^{2+}, Fe^{3+}, and Al^{3+} in the clay aqueous leachates. All antibacterial clay samples contain Fe^{2+} and buffered solutions to pH (2.5–3.1) and oxidizing Eh (630–706 mV) conditions.

Londono and Williams 2015, evaluating the antibacterial action of a clay of lacustrine origin from the Colombian Amazon, in which smectite and halloysite are the dominant clay minerals, have compared the chemical composition of *Escherichia coli* and of the AMZ clay after their inter-reaction and found out that *E. coli* had adsorbed and increased the contents of some metals (Fe, Cu, Ni, Zn, Al, P), mainly Al^{3+}, liberated from the clay dissolution under acidic pH (4.5) conditions. The authors take into account that Al^{3+}, whose ionic radius is significantly smaller than the ionic radius of Fe^{2+}, could replace Ca^{2+} and Mg^{2+} in bacteria membrane and due to its chemical affinity with phosphate ligands could alter lipid-protein interactions when it is bound to phospholipids (Garcidueñas-Pina and Cervantes 1995). Also, Al^{3+} could interfere too with the membrane electrical potential inhibiting membrane transport proteins (Xu et al. 2012), and in acidic conditions, the displacement of membrane cations by H^{1+} would compromise membrane integrity leading to cytoplasm leakage.

Ghadiri et al. 2015, enhance the antimicrobial activity of some cationic clay minerals.

Morrison et al. 2016, showed that in the clay deposit located in Oregon Cascade Mountains, near Crater Lake, in the USA, marketed by OMT (Oregon Mineral Technologies), the clay from the blue zones derived from volcanogenic hydrothermal alteration, along a fault, of andesite porphyry and volcaniclastic rocks, destroys a broad range of human bacterial pathogens, including antibiotic-resistant strains, through the synergistic actions of Fe and Al. Fe toxicity appears to be enhanced by Al that promoting changes and damage on the structure of bacterial membranes favors permeability and oxidation (Zatta et al. 2002). And, Morrison et al. 2017, disclose more detailed geological, mineralogical, geochemical, and microbiological data of the OMT clay deposit and studied and discussed the correlations being found between mineralogy and chemistry and the antibacterial activity of specific clays from the deposit referred to. The bactericidal activity was found just in pyrite-bearing clays which pH (<4.2) and Eh > 600 mV, factors that after clay rehydration in de-ionized water determine the driving of mineral dissolution and metal hydrolysis to produce Fe^{2+} and Al^{3+} and hydroxyl radicals, are essential to kill bacteria, the pH and Eh of hydrated clay being important for stabilizing the aqueous reactants. However, pyrite-bearing clays with pH values within 4.2–4.7 and Eh values >400 mV just cause bacteria growth inhibition.

Wang et al. 2017, have attempted to understand and explain the mechanism of action of the antibacterial clays bearing reduced agents, particularly Fe^{2+} in illite and smectite groups of clay minerals including *illite*, *montmorillonite*, *nontronite*, and *rectorite*, the so-called reduced iron-containing clays (RIC). The authors have studied and discussed the bactericidal activity against *Pseudomonas aeruginosa* and *Escherichia coli* of chemically reduced illite and smectite clays bearing significant amounts of Fe^{2+}.

Soluble Fe^{2+} was considered as a critical antibacterial agent in natural antibacterial clay minerals, and that structural Fe^{2+} which produces lethal hydroxyl radicals, OH, at near neutral pH, and other reactive oxygen species (ROS) upon its oxidation in air is critical too. It had been found out the importance of ROS in attacking cell membrane, intercellular penetration of soluble Fe^{2+}, and its subsequent oxidation to produce OH that damage intracellular proteins. Also, Londono et al. 2015, 2017, had found out that the antibacterial action against *Escherichia coli* of the kaolinite-rich lacustrine clay from the Colombian Amazon could be attributed to free Al, since only Al derived from the clay exceeded the minimum inhibitory concentrations for *E. coli* under acidic conditions. Besides Al, the clay chemical analysis has identified P and the transition metals Fe, Cu, Mn, and Zn. Ion imaging tests showed elevated Al levels in the bacterial membrane and high intracellular Fe levels, compared to those found on untreated controls.

Williams 2017 presents a very interesting review that updates all existing information on antibacterial clays, in order to understand the factors and mechanisms of action involved in the elimination of human pathogenic microorganisms. It has been recognized that pH and Eh (the oxidation potential of the clay/water paste) are determining factors for the identification of the antibacterial potential of the clay.

The bactericidal character of certain clays was also recognized by Behroozian et al. 2016, after investigating the antibacterial activity of "Kisameet clay" occurring in a glacial clay deposit of Quaternary age and dark-greenish-gray color that becomes light gray after being dried. The clay deposit called "Kisameet glacial clay" is located about 450 km northwest of Vancouver, British Columbia, Canada.

The group of pathogenic bacteria ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species) that has been identified in Kisameet clay is responsible for the majority of hospital infections caused by bacteria that are becoming increasingly resistant to antibiotics, which have been poorly and overused. Curiously, the name ESKAPE, composed by the initials of the names of the mentioned bacteria, is homophone of the English term "escape" that means to escape to the activity of all the antimicrobial agents available. For hundreds of years and empirically, excellent therapeutic properties have been attributed to "Kisameet clay" in the treatment of diseases such as ulcerative colitis, duodenal ulcer, arthritis, phlebitis, and burns (Hauser 1950, 1952). In vitro experiments performed by Behroozian et al. 2016, have shown that the antimicrobial activity of Kisameet clay is clearly significant in the case of ESKAPE group bacteria.

Svensson et al. 2017, who had previously shown the potent activity against a variety of antibiotic-resistant bacteria of the "Kisameet clay" had studied the geochemistry and the microbiome of this clay, and surprisingly they found in the microbiome the existence of a great diversity of resident bacteria that could act as bio-control agents or producers of novel bioactive compounds. In fact, "Kisameet clay" relatively rich in iron harbors a surprising number of different bacterial species, represented by the following bacterial phyla: *Proteobacteria* (the most represented), *Bacteroidetes*, *Actinobacteria*, *Acidobacteria*, and *Firmicutes*. Based on the studies carried out by the authors, the possibility that particular bacterial species of the resident bacterial communities could contribute through the genetic interaction between microbes to their inhibitory properties should not be ruled out.

In recent years, there has been much interest on the development of materials able to inhibit bacteria growth due to their potential use in everyday products like paints, kitchenware, school and hospital tools, etc., and the inorganic antibacterial materials such as modified clays have clear advantages relative to the traditionally used organic materials, advantages such as chemical stability, thermal resistance, long-lasting action, and safety to the users.

Recent advances in clay research point out that some specific clays possess microbicidal activity in particular for several species of pathogenic bacteria; however, the identification of their active components and action mechanisms still is an endeavor in progress: Williams et al. 2004; Ma'or et al. 2006; Haydel et al. 2008; Williams et al. 2008; Williams et al. 2009; Cunningham et al. 2010; Masurat et al. 2010; Williams et al. 2010; Williams et al. 2011; Otto and Haydel 2013; Williams and Hillier 2014; Londono and Williams 2015; Ghadiri et al. 2015; Behroozian et al. 2016; Morrison et al. 2016; Kalinowski et al. 2016; Panko et al. 2016; Williams 2017; Londoño et al. 2015, 2017; Svensson et al. 2017; and Wang et al. 2017.

As a matter of fact, dozens of scientific articles can be found in the literature describing and investigating the mechanisms of action of the so-called killer clays, which can be a possible new answer to "superbug" infections. "Superbugs" are pathogens or disease-causing microorganisms resistant to multiple antibiotics, and such antibiotic resistance is presently a matter of major public health concern.

One example of "superbug" is the methicillin-resistant *Staphylococcus aureus* (MRSA). "This serious threat is no longer a prediction for the future*"* states a World Health Organization (WHO) report. "It's happening right now in every region of the world and has the potential to affect anyone, of any age, in any country.*"*

The resistance of the "superbug" to the action of multiple antibiotics has very negative consequences in public health. Dozens of scientific articles can be found in the literature describing and investigating the mechanisms of action of the so-called killer clays, which can be a possible new answer to "superbug" infections. "Superbugs" are pathogens or disease-causing microorganisms resistant to multiple antibiotics, and such antibiotic resistance is presently a matter of major public health concern, since the resistance of the "superbug" to the action of multiple antibiotics has very negative consequences in public health (Diekema et al. 2004; Arias and Murray 2009).

According to a very recent (April 2019) report of WHO, the indiscriminate use of antibiotics (particularly of broad-spectrum quinolone antibiotics causing breakage of bacteria chromosomes, which are reckoned as resistance inducers) and the diseases resistant to them are responsible for at least the death of 700,000 people each year, worldwide. Also, about 80% of all antibiotics are used in agriculture and particularly in livestock, and the target of the EC program "Farm to Fork" is to reduce and eliminate from the environment the presence of antimicrobian compounds, a public health problem, really an *antibiotic footprint*.

In Europe, a recent study carried out by the "European Centre for Disease Prevention and Control (ECDC)" reports that every year 33,000 people die due to antibiotic-resistant bacteria, most of the deaths happening in hospitals, the worst scenarios occurring in Italy, Greece, Romania, and Portugal.

In the case of Portugal, the study did estimate, in 2015, 24,021 infections and 1158 deaths. Also, according to OCDE, up to the year 2050, the number of infections attributed to "superbug" could kill 2.4 million of individuals in Europe, North America, and Australia. In Portugal 49,443 deaths are estimated.

The infections attributed to "superbug" are a real menace to modern health systems. However, such menace is not limited to hospitals. The livestock industry has a central responsibility for the fact that antibiotics are becoming ineffective, as 70% of antibiotics in the European Union are used in animal husbandry. For these reasons, it is necessary to restrict the administration of antibiotics, the antibiotherapy, in the sector of animals. Animals that are treated with antibiotics may end up being carriers of bacteria resistant to them, which in turn can be transmitted to the plants through the manure used as fertilizer, and of the produced foods – meat and vegetables – the said bacteria can pass to the humans.

The European Union wants all antibiotics to be exclusively for human use, and there may be legislation preventing the use of antibiotics in a preventive way in animals for human consumption. In the EU, since 2006, the use of antibiotics to stimulate the growth of food industry animals has been banned. In November 2018, the scientific journal *The Lancet Infectious Diseases* published the results of a study involving the 28 (twenty-eight) countries of the EU plus Norway, Iceland, and Liechtenstein, reporting the deaths and damage caused in people that utilizes the Public Health Services of those countries due to "superbug."

Using data for 2015 provided by the European Antimicrobial Resistance Surveillance-Net (EARS-Net), the weighed contribution of five types of infection was assessed, infection in the bloodstream, infection in the urinary tract, infection in the respiratory tract, infection in surgery sites, and other infections; the obtained results indicate 672,000 infections/year ending in 33,110 deaths and loss, due to incapacities, of 875,000 days of healthy life.

Mortality and incapacity affect more babies less than 1 year old and people older than 65, the worse situations happening in Italy, Greece, Romania, and Portugal. In Portugal, the bacteria MRSA (*Staphylococcus aureus*) resistant to methicillin, *Klebsiella pneumoniae*, and *Escherichia coli*, the last two being resistant to various antibiotics of broad spectrum, such as *quinolones*, *cephalosporins*, and *carbapenems*, are the most resistant to antibiotics.

The pandemic due to the new coronavirus *COVID-19* is proving information about what scientists know well: cyclically nature surprises the humanity, and the notice of this new virus emergency is old and not unique. Bacteria can surprise the humanity too. Patients infected with superbugs have been detected in international laboratories, and the appearance of pandemics is a question of time. Bacteria are developed in vitro for which no antibiotic is efficacious. This really means a latent pandemic, although an answer in vitro is different from an answer in vivo. Two mechanisms are known that provide bacteria multiresistance: adaptative and mutational (of proper genoma enabling the production of an enzyme that inhibits the antibiotic action). There are two bacteria *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* which are evolving to "invincible" forms. The first bacteria appeared about 20 years ago caused multiresistant *tuberculosis*, and many people have died. Portugal is one of the countries where the prevalence of the two multiresistant bacteria referred to is high in hospital environment, 11% of *Klebsiella* (in Italy 40% and in Greece 50%) and 20% of *Pseudomonas*. These bacteria still are not disseminated in the communities, but it is high the transmission risk to the hospital external environment.

The real menace of pathogens associated with human infection justifies the recent research being carried out with great expectation and apparent success of the "predatory therapy" that involves the use in vivo of innocuous "good bacteria," specifically strains of *Micavibrio aeruginosavorus* and *Bdellovibrio bacteriovorus* to kill "bad bacteria" of the gram-negative group (Dashiff et al. 2011; and Harini et al. 2013).

Panko et al. 2016, have investigated the physicochemical and microbiological properties of Black Sea mud/peloid and found out that mud/peloid microbiocenosis has the ability for self-purification and regeneration of its composition; the high content of nitrifying and iron-oxidizing aerobic bacteria would justify the antimicrobial effect for *E. coli* that has been incubated in the mud suspension with an infective dose of 10^6 CFU/cm^3.

Bacteria communities are common in soils, and, naturally in clays, the bacterial diversity is dependent upon pH, higher diversity occurring for neutral pH than for acid or basic pH (Flerer and Jackson 2006).

Adusumilli and Haydel 2016 have evaluated the in vitro antibacterial activity of a panel of clay mixtures and their derivative leachates against *M. ulcerans* and assessed the in vivo efficacy of topically applied hydrated clays on *Buruli ulcer* progression in mice infected with *M. ulcerans*. The research being carried out revealed that specific clays that exhibit in vitro bactericidal activity against gram-negative and gram-positive pathogens also exhibit in vitro bactericidal activity against *M. ulcerans* and that hydrated clay poultices may offer a complementary and integrative strategy for topically treating *Buruli ulcer* disease.

Recently Zarate-Reyes et al. 2017, report the compositional factors associated with the antimicrobial activity of certain clay sampled in Brannenburg, Germany, where it dominates the clayey mineral *Fe^{2+}-saponite*. The authors showed that the clay was active against gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella*, and *Klebsiella pneumoniae* and not active against gram-positive bacteria. In another article, Zarate-Reyes et al. 2017, show the bacteriostatic character of *Escherichia coli* of the magnesium mineral called brucite.

In the last few decades, clay minerals have been considered as efficient carriers of active drug molecules, aiming toward applications in the medical industry.

Clay minerals or modified clay minerals can be used also as carriers of antibacterial drugs. Holesová et al. 2006, did study the antimicrobial activity of kaolinite and kaolinite nanocomposites against bacteria strains *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, and the authors did find out that particularly the prepared nanocomposites carrying *chlorhexidine dihydrochloride* as antimicrobial agent were very effective. The development of suitable materials with the ability to inhibit the growth of microbes is one of the current topics of medical research. For instance, diseases that affect the oral cavity such as oral candidiasis and periodontal diseases are considered a significant public health problem. A solution might be offered by anchoring the drug to a suitable carrier that can provide transport to the designated place in the body, gradual release, and hence suppression of side effects.

Organoclays are a large group of hybrid materials of various types based on clay minerals modified with organic compounds, and most common organoclays contain cationic surfactants, most often of the alkylammonium type. Quaternary alkylammonium cations are a group of organic compounds which are suitable for modifying the surface properties of clay minerals.

Quaternary ammonium salts are industrially used as broad-range antimicrobial and disinfection agents determined to also exhibit activity against resistant bacteria (Yuen et al. 2015).

Bujdáková et al. 2018, have tested the antibacterial properties and physicochemical characteristics of organoclays based on *montmorillonite* and quaternary alkylammonium and phosphonium cations, their activity being tested on the gram-positive bacteria *Staphylococcus aureus* and the gram-negative bacteria *Escherichia coli*.

The antimicrobial effect of *montmorillonite* alone was negligible, but the organoclay having dodecyltrimethylammonium cation reduced the survival of both *S. aureus* and *E. coli* by over 93%.

It is possible to provide antibacterial properties to inert materials by treating them with metallic ions with bacteriostatic nature, such as silver (Ag), copper (Cu), and zinc (Zn). Few examples are given below.

Using modified clay minerals, Garshasbi et al. 2017, have tested comparatively the antibacterial properties of ZnO/nanoclay hybrids (made of montmorillonite immersed for some time into ZnCl at 350 and 450 °C) against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* bacteria. The results suggest that the hybrid had a toxic effect on the bacteria, most probably associated with the photocatalytic mechanism of nano-ZnO, which generates hydrogen peroxide and causes the degradation of the membrane structure of the bacteria. Using modified clay minerals, Garshasbi et al. 2017, have tested comparatively the antibacterial properties of ZnO/nanoclay hybrids (made of montmorillonite immersed for some time into ZnCl at 350 °C and 450 °C) against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* bacteria. The results suggest that the hybrid had a toxic effect on the bacteria, most probably associated with the photocatalytic mechanism of nanosize *zincite*, ZnO, which generates hydrogen peroxide and causes the degradation of the membrane structure of the bacteria.

Pourabolghasem et al. 2016, have investigated the antibacterial activity of Cu-doped montmorillonite nanocomposites, the copper-loaded clay nanocomposites being synthesized by alkaline ion exchange processes in media containing copper sulfate at 550 °C. The antimicrobial effects of Cu-doped montmorillonite powders against pathogen bacterial strains *Escherichia coli* and *Staphylococcus aureus* were tested in broth media, and the results were positive with high mortality, 99.98% against *E. coli* and 100% against *S. aureus*. The *montmorillonite* alone had no antibacterial activity.

Syafawani et al. 2016, have used kaolinite as the support and carrier of Cu^{2+}, selected as the antibacterial agent against gram-positive bacteria (*S. aureus* and *E. faecalis*) and gram-negative bacteria (*E. coli* and *P. aeruginosa*). The authors found out that Cu^{2+}-kaolinite which had been prepared after being treated with $CuNO_3.3H_2O$ becomes still more active after the clay mineral was modified with a cationic surfactant. Also, Ye et al. 2003; Tong et al. 2005; and Hu and Xia 2006, have tested with success the antibacterial effects of the Cu (II)-exchanged montmorillonite on *Escherichia coli* K88 and *Salmonella choleraesuis*.

Morones et al. 2005, have shown the bactericidal effect of silver (Ag) nanoparticles.

It is acknowledged that pollution and contamination by microorganisms can be interrupted and eliminated using certain organic and inorganic chemical agents and certain physical agents too (heat, UV light, ionized radiations).

Within the inorganic bacteriostatic and bactericidal agents, some deserve particular emphasis: certain metals/ions such as Ag, Cu, Zn, and Au; certain metal oxides such as TiO_2, ZnO, CuO, FeO, and MgO; and certain clays. These substances can inhibit microorganisms growth acting as *bacteriostatic* agents or disrupting bacteria cell membranes acting as *bactericidal* agents.

7.5.2 Other Microbicidal Minerals

Not only clay can show microbicidal activity. For instance, some specific Fe-bearing minerals, such as *pyrite*, FeS_2, have proved highly reactive in water sanitation both in the form of slurries and in the form of leachates (Friedlander et al. 2015). However, the authors have demonstrated in the case of the bacteria *Escherichia coli* that *pyrite* leachate is more effective than *pyrite* slurry.

Ferrous iron in solution drives the bacterial elimination and a steady production of ROS (reactive oxygen species). Also, *pyrite* oxidation by acid (H_2SO_4) treatment produces OH radicals. For the authors, ROS may disrupt the cell membrane of the bacteria, while Fe^{2+} in solution infiltrates and overwhelms the cell. Anyway, the experiments have shown the importance of chemical interaction relative to physical interaction in bacterial elimination. The chemical drives resulting from *pyrite* dissolution are $Fe^{2+}{}_{(aq.)}$, ROS, and acidity.

$$2FeS_2 + 7O_2 + 2H_2O \rightarrow 2Fe^{2+}{}_{(aq.)} + 4SO_4{}^{2-}{}_{(aq.)} + 4H^+$$

Regarding acidity, *pyrite* dissolution yields pH = 3, and the experiments carried out by Friedlander et al. 2015, and Cunningham et al. 2010, point out that pH is not the driving factor of *pyrite*'s bactericidal properties.

Worldwide, diarrheal diseases are the second most common cause of death for children under 5 years old, these diseases being attributed to drinking water contamination by four pathogens (*Rotavirus*, *Cryptosporidium*, enterotoxigenic *Escherichia coli*, and *Shigella*).

Water disinfection is the removal, deactivation, or killing of pathogenic microorganisms existing in water. Clays and modified clay minerals are reckoned as good adsorbents for bacteria removal in water, reason why they are used in wastewater treatment and environmental bioremediation, due to large surface areas and surface charge (Yuan et al. 2013). The use of modified clay-polymer composites for removal of bacteria in water has been extensively discussed (Unuabonah and Taubert 2017).

Morrison et al. 2017, after having studied the antibacterial activity of several types of clay, *pyrite*-bearing, non-sulfide-bearing, and red oxidized clays from Cascade Mountains, Oregon, USA, found the greatest antibacterial activity for *pyrite*-bearing clays compared to non-sulfide-bearing white clays and did find also that red oxidized clays do not exhibit antibacterial activity. Unuabonah et al., 2017, have shown the bacteriostatic character of clay composites.

Very recently, in the USA, two patents of inventions have been applied, one entitled "Synthetic antibacterial clay compositions and method of using same" and the other entitled "Antibacterial clay compositions for use as a topical ointment," both being published under the references US2013/0004544A1 and US2018/0021374A1, respectively. Meanwhile, the first application has been abandoned, improved, and replaced by the second application.

The scope of the first patent application by the inventors Metge DW, Williams L, Eberl DD, Blum AE, and Harvey RW is the use of synthetic bactericidal compositions having clay-like properties and a method of using these compositions to topically treat bacterially caused skin infections and skin diseases. The scope of the second invention applied by the inventor Tuba T is also the treatment of bacterially caused skin infections and skin diseases, the pH being a determinant factor for rendering the clay bactericidal.

When natural clays reveal antibacterial properties, these are attributed to reducing agents, as a rule making Fe^{2+} part either of the structures of clay minerals (particularly of smectite-rich clay minerals) or of external compounds, natural or synthetic. The inventions referred to mention the preparation of pastes by mixing clay or clay minerals, natural or synthetic, with water and reducing agents such as the minerals *pyrite* (FeS_2) and its polymorph *marcasite* (FeS_2), *pyrrhotite* ($Fe_{1-x}S$, where $x = 0–0.2$), *melanterite* ($FeSO_4.7H_2O$), as well as the synthetic salt $FeSO_4$.

Photos-Jones et al. 2015, studied and confirmed the antibacterial properties of Samian's earth occurring in the Greek island Samos, in the Aegean Sea, whose pharmacological action had already been recognized by Dioscorides (In: *Matter of Medical Matter*, book V, 172), by Galenus (In: *De Simplicium Medicamentorum*), and by Pliny (In: *Historia Naturalis*, book XXXV). Dioscorides referred to the existence of two varieties of Samian's earth, the variety called collyrion used as a medicament for eye affections and the variety called aster used in the laundry sweep.

Geological, mineralogical, and chemical studies conducted by Photos-Jones et al. 2015, have identified *colemanite*, $Ca_2B_8O_{11}.5H_2O$, and *ulexite*, $NaCaB_5O_9.8H_2O$, boron minerals, and the boron element could occur in clay at concentrations up to a few thousand ppm. The same authors tested preparations in which cultures of *Staphylococcus aureus* and *Pseudomonas aeruginosa* were added to the clay and concluded that the bactericidal effect identified for the two pathogenic microorganisms resulted from the presence and action of boron (B) in the form of boric acid, $B(OH)_3$, rather than the nature of the clay.

Milenkovic et al. 2017, have demonstrated the bactericidal activity of Cu^{2+}-, Zn^{2+}-, and Ag^{+}-containing zeolites, both natural (*clinoptilolite*) and synthetic (*zeolite-A*), toward *Escherichia coli* isolates in three distinct water media (peptone water, commercial spring water, lake water). The authors had found out that it is the metal type and not the zeolite type which is responsible for the antibacterial activity and that the antibacterial activity is not attributed to cytoplasmic membrane damage.

Two zeolites, one natural, *clinoptilolite*, and the other synthetic, *zeolite-A*, have been used and enriched in Cu^{2+}, Zn^{2+}, and Ag^{1+} ions. It has been found the following order for the antibacterial activity of the tested ions: Ag > Cu > Zn, 100% reduction being achieved using Ag-zeolites. This powerful antibacterial activity of Ag-zeolites had been already demonstrated by other researchers such as Hrenovic et al. 2013, 2013, and Demirci et al. 2014.

The porous structure of zeolites enables metal cations to move freely, and this seems to be responsible for their bactericidal activity (Kwakye-Awuah et al. 2008). The antibacterial activity of metal-zeolite compositions had been demonstrated by other authors (Feng et al. 2000; Top and Ulku 2004; Jung et al. 2008; De la Rosa-Gomez et al. 2008; Ferreira et al. 2012; Lemire et al. 2013; Rossainz-Castro et al. 2016).

Zarate-Reyes et al. 2017, show the *bacteriostatic* character of *Escherichia coli* of the magnesium mineral called *brucite*, $Mg\ (OH)_2$, mineral in which Fe can replace a small part of Mg. Also, Bui et al. 2016, have demonstrated that bentonite from Tam Bo deposit, in Vietnam, modified with Ag (silver) nanoparticles can effectively inhibit the growth of opportunistic pathogens like *Enterococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Candida albicans*.

Only few and specific clays and clay minerals have bactericidal capacity. However, the generality of clays and clay minerals has the adsorption capacity of bacteria and viruses at their large and electrically charged surfaces, capacity very useful, for instance, as aforesaid in the purification of water used for human consumption (Unnabonaha et al. 2018). Also, very recently Pardo et al. 2020, showed how clays and clay minerals as well as clay-based materials such as PC (porous clay heterostructures) could efficiently remove one of the most dangerous bacteria that could be found in drinking water, *Salmonella* spp., gram-negative bacilli.

7.5.3 Bactericidal Peloids

Author's interest on bacteriostatic/bactericidal clays was risen on the course of their studies and experiences on *peloids*. In terms of general composition, there are similarities between the clay/water systems used for bacteriostatic/bactericidal purposes and the clay/water systems called *peloids* used in therapeutic/cosmetic topical applications within the medical field of *peloidotherapy* or *pelotherapy* and practiced inside the balnearies and other facilities of thermal centers and spas (Gomes et al. 2013; Gomes 2015; Gomes 2018).

In both the aforesaid systems, it is the liquid phase and not the solid phase that is the major responsible factor for the medicinal/cosmetic properties, justifying the fact of *peloids* being studied and applied within the scope of the scientific field medical hydrology, particularly in the treatment of rheumatic diseases, such as osteoarthritis and low back pain.

Peloids are three-component semi-solid systems, a solid phase (normally clay), a liquid phase (normally thermal mineral water), and a gas phase (normally SH_2, CO_2, and radon). The main properties of the peloid solid component, in general consisting of clay, are as follows: mineralogical composition, chemical composition, particle size distribution, and particle shape. And, the main properties of the peloid liquid component are as follows: chemical composition and temperature.

Naturally are the properties of both solid and liquid components which essentially determine *peloids*' relevant properties: viscosity, adhesiveness, abrasiveness, spreading, heat capacity and specific heat, cooling rate, bioavailable chemicals, and cation and anion exchange capacities. However, it is the peloid liquid component properties due to the nature and composition of the natural mineral water from spring sources or from deep settled boreholes, seawater, or salt-lake water, particularly the nature and concentration of the electrolytes present in it and their interaction with the skin, which are greatly responsible for *peloids*' medical/cosmetic interest.

A quite significant number of articles have been produced in recent years on *peloids*' characterization, function, and application, and just few are herein referred to: Delfino et al. 2003; Dreno 2004; François et al. 2005; Costantino and Lampa 2005; Costantino 2006; Veniale et al. 2007; Bellometti et al. 2007; Evcik et al. 2007; Fioravanti et al. 2011; Espejo-Antúnez et al. 2013; Maraver 2013, 2017; Gomes et al. 2013; Baschini et al. 2014; Fioravanti et al. 2014; Roques 2015; Gomes 2015; Fioravanti and Chelesschi 2015; Centini et al. 2015; Rautureau et al. 2017; and Gomes 2018.

Peloids, as a rule, are directly applied onto the skin, reason why they should be sanitary safe, both chemically and microbiologically. For cosmetic peloids, there are in Europe qualitative and quantitative guidelines that guarantee their sanitary safety against pathogenic microorganisms (European Standard EN ISO 17516:2014 Cosmetics-Microbiology-Microbiological Limits), but the same does not happen so far for therapeutic or medical peloids, which are particularly used in balneological treatments of rheumatic disabilities.

Naturally, it would be rather important to have available medical peloids free of pathogens and even, in particular cases, *bactericidal peloids*. The authors have carried out studies on both natural and modified clay systems interesting on the author's perspective for the preparation of pathogens' safe therapeutic and cosmetic *designed and engineered peloid*, a type of *extemporaneous peloid* based on simple and chemically/microbiologically controlled composition, consisting of clay of simple composition and distilled and sterilized water or medicinal thermal water. The experimental work the authors have carried out so far point out to the viable development of *bacteriological safe peloids and bactericidal peloids* able to treat particular infectious skin disorders.

As a natural system, one natural clay classified as *heavy clay* was used, clay with great tradition on ceramic applications, more precisely for brick and roof tile production. Such clay with reference A-Campos that exhibits blue-green color, is very finely grained, and is highly plastic had been collected in an occurrence included in the geologic formation named Clays of Aveiro-Ílhavo-Vagos, dated of Upper

Table 7.3 Major chemical elements of clay A-Campos expressed in weight percentage

SiO_2	Al_2O_3	TiO_2	FeO	Fe_2O_3	MgO	CaO	MnO	K_2O	Na_2O	P_2O_5	SO_3	LOI
55.56	19.99	0.79	4.90	1.67	2.28	0.46	0.03	6.15	0.22	0.04	0.08	7.59

Note: About 75 % of Fe is in the Fe^{2+}state; *LOI* Loss on Ignition

Table 7.4 Major chemical elements of clay A-130 expressed in weight percentage

SiO_2	Al_2O_3	TiO_2	Fe_2O_3	MgO	CaO	MnO	K_2O	Na_2O	P_2O_5	SO_3	LOI
46.23	37.07	0.60	1.41	0.28	0.02	0.03	1.23	0.07	0.13	0.04	12.75

Note: All Fe is in the Fe^{3+} state; *LOI* Loss on Ignition

Cretaceous, occurrence located very close to the center of the town of Aveiro, Portugal. The clay without manipulation, in terms of refining and beneficiation, was mineralogically and chemically studied.

In terms of mineralogical composition that was determined by X-ray diffraction (XRD), the clay A-Campos is mainly composed of dioctahedral and trioctahedral illite and of smectite. Kaolinite is a minor constituent (<10%), smectite makes 20%, and illite makes about 70% of the total mineral content.

Table 7.3 shows the chemical data of clay A-Campos corresponding to major chemical elements, data expressed in weight percent.

The quantification of minor and trace elements of clay A-Campos has provided the following data expressed in ppm: Cl, 80; F, 65; V, 60; Cr, 51; Co, 9.5; Ni, 22; Cu, 16; Zn, 34; As, 5; Br, 3; Sr, 67; Pb, 27; Th, 16; and U, 3. Specific surface area (SSA), $95m^2g^{-1}$, and cation exchange capacity (CEC), 60 meq/100 g, are the values estimated in A-Campos clay for these two very important properties.

As a modified and artificialized system, one other clay with reference A-130 clay classified as commercial kaolin with origin in the Alvarães kaolin deposit, near the town of Viana do Castelo, north of Portugal, was selected and studied. Unlike the A-Campos clay, the A-130 clay had been submitted to industrial processing in order to reduce grain size and concentrate kaolinite, its essential clay mineral.

The mineralogical composition clay A-130 with grain size less than 45 μm is mainly composed of kaolinite-D, i.e., disordered kaolinite, plus dioctahedral mica/illite, kaolinite-D making about 85% of the clay mineral's total content, dioctahedral illite making around 7%, and other minerals (mainly quartz) making about 8%.

Table 7.4 shows the chemical data of clay A-130 corresponding to major chemical elements, data expressed in weight percent.

The quantification of minor and trace elements of clay A-130 has provided the following data expressed in ppm: V, 38; Cr, 35; Co, 5; Ni, 9; Cu, 9; Zn, 27; Ba, 20; Sr, 13; Sb, 2; Pb, 12; Th, 23; and U, 6. Specific surface area (SSA), $30m^2.g^{-1}$, and cation exchange capacity (CEC), 18 meq/100 g, are the values estimated in A-130 clay of these two very important properties.

Two compositions or formulations were prepared based on each one of the two distinctive types of clay aforesaid referred to and analyzed.

In the first composition, an *illite-smectite-kaolinite* clay and distilled water were properly blended yielding a consistent paste. Such clay with reference A-Campos contains Fe^{2+} constituent of both *illite* and *smectite* clay minerals and located in their octahedral sheets, element assumed to be an effective reducing agent. A-Campos clay shows physicochemical properties similar to those shown by the so-called French green clay that as aforesaid could be bactericidal. Unlike in the first composition, in the second composition, one almost monomineralic kaolin clay was used. This clay with reference A-130 is one industrial kaolin in which kaolinite, being its fundamental clay mineral, is exempt of any reduced metal. Also unlike in the first composition, the clay was previously sterilized. The clay was blended with distilled water till the formation of a consistent paste, and from it, a sample was taken to which a Fe^{2+}-bearing reducing agent, synthetic $FeSO_4$, was added.

In both the aforesaid very distinctive compositions, the pH was controlled along the composition processing. Very low (<4) or very high (>9) pH value could be by itself a bactericidal factor, acidic or basic pH being a required condition for the extraction of Fe^{2+} from the clay mineral structures in the case of A-Campos clay and from $FeSO_4$ in the case of A-130 clay, making it bioavailable, condition also required to keep Fe in the reducing form.

Three bacteria strains, *Pseudomonas aeruginosa* 67p, *Staphylococcus aureus* ATCC 6538, and *Escherichia coli* ATCC 25922, were used in the tests carried out. For test control, one disk with com 5 µg of antibiotic (CIP, ciprofloxacin) was used.

Test strains (0.5 McFarland inoculum) were inoculated into 90 mm Petri dishes with Mueller-Hinton agar and in triplicate. A sample of the material to be tested (50–80 mg of paste made of kaolin A-130 previously sterilized by heating at 200 °C during 1 hour + distilled water + $FeSO_4$) and a sample of antibiotic (ciprofloxacin) were subsequently placed in each of the disks.

The plates, one to which the three-component composition of kaolin A-130 was given the reference CAUF and the other corresponding to the antibiotic to which the reference ANTIBIO was given, were both wrapped in aluminum foil and incubated at 37 °C for 18 h.

Figure 7.7 shows images relative to the evaluation of the antibacterial activity of the three-component composition corresponding to kaolin A-130.

The appearance of a zone without growth around the disk/sample is indicative of a positive action (material with antibacterial activity). The diameter of that zone of inhibition is related to the ability to inhibit (a larger diameter indicates superior antibacterial activity). Zones of inhibition were detected in the kaolin sample tested for all strains tested. The diameter of these zones ranged from 19 to 29 mm. Results for control (CIP) were as expected, i.e., all strains showed susceptibility to ciprofloxacin.

As a conclusion of the experimental work the authors have carried out so far with the aforesaid composition based on three components, easily a *bacteriological safe and bactericidal peloid* could be developed, able to treat particular infectious skin disorders. And, as a conclusion too of the experimental work being carried out so far, the authors consider that clay can play a threefold role in bactericidal compositions:

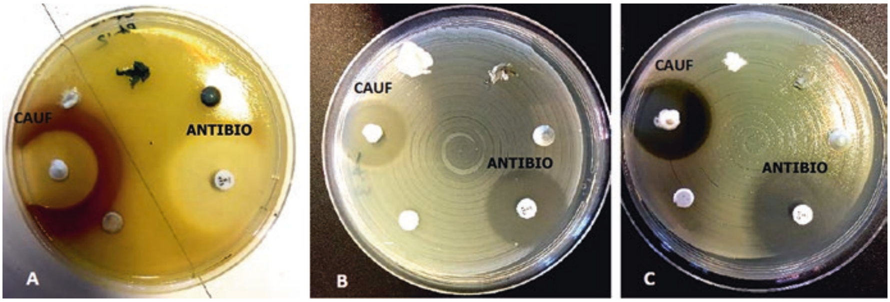


Fig. 7.7 The images show the results of the evaluation of the antibacterial activity of the CAUF and ANTIBIO samples against the strains: *Pseudomonas aeruginosa* (**a**); *Staphylococcus aureus* (**b**) and *Escherichia coli* (**c**)

1. Clay is simply a vehicle or carrier of the bactericidal reducing agent, either just fixed in the ion form at the surfaces of the clay mineral particles taking advantage of the high specific surface area, electric charge, and ion exchange capacity of the clay minerals or as an associate component of the clay natural composition, for instance, reducing Fe-bearing minerals, such as *pyrite* (FeS_2), marcasite (FeS_2), *pyrrhotite* (Fe_{1-x} S), and *arsenopyrite* (FeAsS).
2. Clay is an active bactericidal player in case one or more than one of their constituent clay minerals bear in their crystallochemical structures reducing agents that could become free through mineral dissolution that can occur in case clay is rehydrated, and the leachate shows very low (<4) or very high (>9) pH values.
3. Clay, natural, manipulated and modified, or synthetic, not containing reducing agents in its composition, therefore not exhibiting antibacterial properties, can acquire bacteriostatic or bactericidal properties if a reducing agent, natural or synthetic, is added to the clay and is properly mixed with it.

In any one of the three cases referred to, the antibacterial activity can be exhibited, either by the compositions themselves or just by their leachates. Clay with reference A-130 is clearly an example of bactericidal activity classified into the **type 3** referred to, whereas clay with reference A-Campos is clearly an example of bactericidal activity classified into the **type 2** referred to.

Studies go on considering the effect of variables such as pH, Eh, and reducing agent nature (particularly minerals bearing transition metals other than Fe, for instance, Cu associated with Fe in *chalcopyrite*, $CuFeS_2$; Cu in *covellite*, CuS; and Zn in *sphalerite*, ZnS), incorporated into the compositions, either in solution or in slurry prepared with clay (bentonite and kaolin)/water (distilled and mineral-medicinal) mixtures. Aqueous leachates of the corresponding compositions will be studied too.

7.5.4 Bactericidal Ointments Based on Clay for the Treatment of Infectious Skin Wounds

Going back to *designed and engineered peloids*, they anxiously could be exempted of both pathogens and toxic metals.

The authors have developed a *designed and engineered peloid* in which composition the size fraction less than 45 μm of the A-130 Portuguese commercial kaolin exempt of potentially toxic metals previously sterilized was mixed with medicinal thermal water (sodium bicarbonate sulfurous, 68 °C at the emergence, pH 8.5) of the Portuguese São Pedro do Sul spa, in a 50/50 weight proportion.

Similar composition was also developed using the size fraction less than 10 μm of the aforesaid kaolin to produce an *ointment* able to be used for healing skin infectious wounds common, for instance, in feet and legs of diabetic people (Gomes et al. 2019; Gomes et al. 2020).

Dozens of scientific recent articles can be found in the literature describing and investigating the mechanisms of action of the so-called killer clays which can be a possible new answer to fight the so-called "superbug" infections.

Clay is one of the oldest earth materials used for healing purposes that continues to be applied in modern life to treat various external or topical and internal ailments.

Clay bactericidal character only exists if clay is in the hydrated state and contains bactericidal agents like reduced metals. Reduced Fe^{2+} within other metal species (e.g., of Ag and Zn) whenever existing or added to clay/water pastes might turn them *bacteriostatic* and *bactericidal*.

In clays Fe^{2+} and Fe^{3+} are common structural constituents of clay minerals. In the very white kaolin A-130 kaolin used in our assays, Fe is an almost trace constituent that just occurs as Fe^{3+}. Therefore, the required Fe^{2+} for the preparation of both bactericidal peloid and ointment came from the 1% solution of the synthetic salt $FeSO_4$ added to the paste of kaolin/thermal mineral water afterward duly homogenized.

The bactericidal activity of the *ointment* referred to was tested in three bacteria strains: *Pseudomonas aeruginosa* 67p, *Staphylococcus aureus* ATCC 6538, and *Escherichia coli* ATCC 25922.

Naturally the healing assets of both *bactericidal peloid* and *ointment* being experimentally produced require clinical evaluation. In 2007, the French physician Charrié JC produced a clinical study concerning serious dermatological infections treated with clays which gave excellent results.

Very recently Gomes et al. 2020, produced a review paper entitled "Bacteriostatic and Bactericidal Clays: An Overview" contemplating all the aforesaid information. One relevant and singular issue being focused in this paper is the ability to modify and provide bactericidal activity to non-bactericidal clay characterized by chemical and physical properties appropriate for therapeutic and dermocosmetic applications, for instance, to treat skin infectious wounds. Such modification, still undergoing further developments, has been exemplified using natural kaolin mixed with thermal natural mineral water in the preparation of extemporaneous peloids, more precisely designed and engineered peloids, and ointments too.

In the University of Aveiro, experiences are being carried out using mixtures of a nanoclay (manipulated natural kaolin turned into bactericidal) and mineral-medicinal water (~10% w/w) under the form of *hydrogels* that could be used to treat chronic wounds, for instance, in diabetic foot ulcers, which treatment sometimes involves amputations and implies huge costs (Nussbaum et al. 2018).

A recent study has been reported involving *hydrogels* based on mixtures of apparently no bactericidal nanoclay and mineral-medicinal water. It is the case of fibrous nanoclays based on *sepiolite* and *palygorskite* (Garcia-Villén et al. 2020).

Experiences using mud from Dead Sea applied on rats having skin wounds, and with apparent success, have been conducted by Dário et al. 2014.

7.6 Diseases which Etiology Is Attributed to Clay

In some environments and conditions, some clays and clay minerals may cause more or less serious diseases to man, some being below described.

7.6.1 Podoconiosis

Podoconiosis (from the Greek words for foot, *podos*, and for dust, *konos*), also known as "endemic non-filarial elephantiasis" and as "big foot disease," is a tropical disease caused by exposure of bare feet to irritant clay soils. This disease causes an asymmetrical swelling of the feet and lower limbs due to *lymphedema*. Over the years, the increase in the leg diameter persists and can progress to severe elephantiasis-like disease. The causes of podoconiosis and elephantiasis are quite different.

Elephantiasis, called the neglected tropical disease, is an infection caused by parasitic worms spread in humans and from person to person through female mosquito bites. The worms nest in the lymph nodes grow into big balls that stretch the glands and prevent the lymph fluid from being pumped out of the legs, arms, breast, and scrotum making their swelling.

WHO (World Health Organization) estimates 40 million people disabled by the disease, called lymphatic filariasis. The disease is common in some Asian countries such as India, Indonesia, and Sri Lanka and in some African countries such as Tanzania, Uganda, and Kenya. Fig. 7.8 shows images of *podoconiosis*.

According to Deribe et al. 2018, *podoconiosis* is one of the few diseases that could potentially be eliminated within one generation. Nonetheless, the global distribution of the disease remains largely unknown. The global atlas of *podoconiosis* was conceived to define the epidemiology and distribution of the disease. The authors had identified 3260 records, of which 27 studies met the inclusion criteria. *Podoconiosis* was described to exist or be endemic in 32 countries, 18 from the African Region, 3 from Asia, and 11 from Latin America.

Fig. 7.8 Images of podoconiosis

Overall, *podoconiosis* prevalence ranged from 0.10% to 8.08%, was highest in the African region, and was substantially higher in adults than in children and adolescents. The highest reported prevalence values were in Africa (8.08% in Cameroon, 7.45% in Ethiopia, 4.52% in Uganda, 3.87% in Kenya, and 2.51% in Tanzania). In India, a single prevalence of 0.21% was recorded from Manipur, Mizoram, and Rajasthan states. None of the Latin American countries reported prevalence data. Based on the data the authors had collected, they suggest that *podoconiosis* is more widespread in the African region than in the rest of the regions, although this could be related to the fact that most *podoconiosis* epidemiological research has been focused in the African continent.

The assembled dataset confirms that comprehensive *podoconiosis* control strategies such as promotion of footwear and personal hygiene are urgently needed in endemic parts of Africa. Mapping, active surveillance, and a systematic approach to the monitoring of disease burden must accompany the implementation of *podoconiosis* control activities. In countries of the EARV (East African Rift Valley), such as Ethiopia, Kenya, Tanzania, and Uganda, characterized by profuse volcanism which eruptions produce volcanic rocks, often of alkali-basaltic composition, *podoconiosis* is prevalent in high-altitude areas (>1250 m), of moderate average temperature (20 °C), and high seasonal rainfall (<1000 mm/annually) where reddish-brown clayey soils dominate (Davies 2008). However, *podoconiosis* is not observed in areas characterized by dry climate and sandy soils. Crivelli 1986; Price 1988, 1990; and Fronmel et al. 1993, were the first to consider *podoconiosis* a geochemical disease.

Podoconiosis is an environment-related disease caused by long-term exposure to red clay soil: Price 1972; Price 1976; Price and Bailey 1984;Crivelli 1986; Price 1988, 1990; Fronmel et al. 1993; Nordberg and Cherian 2005; Manderson et al. 2009; Davies 2008, 2010; Davies and Mundlano 2010; Korevaar and Visser 2012; Brevik 2013; Molla et al. 2014; Deribe et al. 2015a; Deribe et al. 2015b; Derbie et al. 2015c; Jones et al. 2015; Tsegay et al. 2016; Buck et al. 2016; Deribe et al. 2017; Davey et al. 2017; Feleke 2017; Deribe 2018; and Lyles 2018.

In endemic areas, *podoconiosis* being a disabling condition, and so often an occupational health issue, it is a considerable public health problem. In local communities, *podoconiosis* is often called "mossy foot disease."

In 2011, the WHO (World Health Organization) designated *podoconiosis* as one of the 20 (twenty) neglected tropical diseases, some like *Buruli ulcer*, *leishmaniasis*, *cysticercosis*, *Chagas disease*, *leprosy*, *fascioliasis*, and *lymphatic filariasis* (*elephantiasis*) being enhanced.

Podoconiosis is a disease of agrarian people who work barefoot, particularly on red clay soil in the neighborhood of volcanoes, either active or inactive. Clay submicron and nanoparticles penetrate the skin of foot and lower limb, and local lymphatics may become obstructed. Those particles enter into the blood through abrasions in the feet and affect the cells of the immune system, the pathogenicity depending on particle enrichment in Fe, Al, and Ti, proper of basic and acid volcanic rocks, alkali basalts, and tuffs.

About 4 (four) million people live with *podoconiosis* globally in 32 potentially endemic countries. *Podoconiosis* is most prevalent in Africa, and especially in the higher altitude regions in the eastern and central part of the continent (Ethiopia, Rwanda, Burundi, Cameroon, Kenya, Uganda, Mozambique, and Tanzania), but the disease also occurs in West Africa (Angola, Equatorial Guinea, Democratic Republic of Congo, Canary, Cape Verde, and São Tomé and Príncipe islands), Central America and northern South America (Colombia, Peru, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, México, and Brazil), northwest India, Indonesia, and Sri Lanka.

Korevaar and Visser 2012, consider *podoconiosis* a neglected tropical disease that has enormous social, psychological, and economic implications for affected individuals. Social stigmatization of people with the disease is widespread, and patients are banned from schools, local meetings, and churches and not allowed to marry into unaffected families.

Using statistical analysis, Molla et al. 2014, showed a positive correlation between *smectite*, *quartz*, and *mica* and the prevalence of *podoconiosis* in northern Ethiopia. The disease begins when mineral particles enter the skin and invade the lymphatic system, and presumably the particles infect or damage the cells.

Jones et al. 2015, assayed the bioreactivity of red clays from basalt weathering in the volcanic island of Madeira, Portugal, that have been shown to cause *podoconiosis*. These clays are mostly composed of kaolinite and iron oxides/hydroxides. They assessed the reaction of the red clays against DNA and different types of human cells and found that the red clays damaged DNA, attacked immune cells, and lysed human blood cells (*hemolysis*). In Madeira's island samples of these red clays we had recently collected in intensively agricultural red clayey soils called *nateiros*, the result of basalt and tuff weathering, are constituted of halloysite nanonspherules and quasi-amorphous iron hydroxides.

Buck et al. 2016, mention some examples of health problems caused by the long-term exposure to geologic materials and processes, within the framework of medical geology, involving, for instance, drinking mineral water, asbestos, and clays. In what clays are concerned, the authors did raise the following question "Are clays friend or foe?"

There are many examples, some mentioned and dealt with in this book, of clay benefits for environment and human health. However, there are few cases of clay threat to human health, well exemplified by the *podoconiosis* disease (severe inflammation of the feet and legs), whose main cause looks to be the long-term exposure to red clayey soils.

7.6.2 Mseleni Joint's Disease, Kashin-Beck's Disease, Keshan's Disease, and Alzheimer's Disease

Mseleni joint's disease (*MJD*) is a devastating endemic osteoarthritic that affects two-thirds of the women, confined to a remote area in the Maputaland Coastal Plain, in northern KwaZulu-Natal, South Africa, and it was clinically named *Mseleni joint's disease* after the Mseleni Mission Station. The earliest studies by Wittman and Fellingham 1970 report an "unusual hip disease" and highlighted its prevalence among adults, with higher incidence in women, and a concentration of cases on the western side of Lake Sibaya near the Mseleni Mission Hospital, in Mseleni.

Gibbson et al. 2010, disclose the natural history of *Mseleni joint's disease*, a crippling endemic osteoarthritis, and its socioeconomic impacts, demographics, diet, geology, and genetic background of affected people are reviewed. In addition, some new research ideas are suggested to continue the search for etiological avenues for this disease such as stable isotope analysis and epigenetic mechanisms. This disease affects most joints but primarily those of the hip; it is a progressive condition beginning with pain and stiffness until the patient's ability to walk becomes compromised.

According to Dinkele et al. 2020, the Mseleni condition is locally known as *unyonga*, meaning a disease of the joints. Individuals with Mseleni joint's disease have chronic joint pain, limited mobility, and inevitably severe physical disability, impacting regional health-care and social welfare systems, which are already heavily burdened by HIV and tuberculosis. The referred to authors consider a multifactorial cause for the disease.

Ceruti 2003 linked this unusual endemic disease to the soil nature, recent Quaternary sands, found to be highly deficient in P, K, Ca, Mg, Cu, and Zn, the deficiency being attributed to the lack of clay in the soil.

Kashin-Beck's disease (*KBD*) is an endemic osteoarthritic disease that, particularly in preadolescent and adolescent, commonly results in serious deformities, muscular dystrophy, and liver necrosis, diseases that primarily occur in a northeast to southwest corridor in central China and in Transbaikal regions of Russia (Cao et al. 2008; Zhang et al. 2010, 2011; and Li et al. 2006). The main features of the disease are shortened stature and joint deformation, resulting from multiple focal necroses in the growth plate of tubular bones.

Zhang et al. 2010, in studies carried out in the Tibetan Plateau where the disease is still active, had achieved the following results:

1. The levels of environmental selenium are very low and the study area belongs to a selenium-deficient ecological landscape.
2. The KBD becomes much more severe with decreasing environmental selenium under the selenium-deficient condition. Namely, the lower the environmental selenium is, the more severe the disease is.
3. Soil selenium deficiency plays a critical role for the prevalence of local KBD, and more factors inducing selenium deficiency should be more concerned in the future.

Kashin's disease (*KD*), an endemic reversible cardiomyopathy occurring in low-selenium areas of China, was reported in 1979 to be responsive to supplementation with sodium selenite. Selenium deficiency is a cause of KD by the criterion of causation in modern epidemiology, reason why selenium should be included in the KD surveillance program (Zhou et al. 2018). The principal pathological finding is multifocal necrosis of the myocardium that causes cardiac enlargement, congestive heart failure, cardiogenic shock, and death. The disease is associated with low selenium intake and low blood and hair levels and affects mainly children and women of childbearing age. It is probably the only case of naturally occurring selenium deficiency (Thomson 2003).

Kashin's disease (*KD*) is named after Keshan County of Heilongjiang province, Northeast China, where symptoms were first noted. These symptoms were later found prevalent in a wide belt extending from northeast to southwest China, all due to selenium-deficient soil. The disease peaked in 1960–1970, claiming thousands of lives. However, a cardiotoxic *coxsackievirus* or another unknown environmental factor has also been implicated as part of the etiology (Beck et al. 2004; Beck 2006; Chen et al. 1980; and Chen 2012).

The treatment for Keshan' disease is selenium supplementation in the form of selenomethionine. The treatment also could involve the consumption of foods rich in selenium in addition to supplements.

According to Finkelman 2019, many studies have recognized the relationship of these diseases to selenium-deficient soils (Tan et al. 2002), but few studies discuss the role of soil clay content, type, or chemistry (Lv et al. 2014).

Nordberg and Cherian 2005 report recent studies indicating that selenium exerts a beneficial effect on coronary disease mortality and the selenium plus garlic produces significant anticancer activity. The authors report countries with soils containing low concentrations of selenium, like Finland, Sweden, and regions of China, and countries with soils with high concentrations of selenium like Scotland, Venezuela, and regions of China.

In this book, Chap. 4, item 4.7.9, the role of Al toxicity in the case of *Alzheimer's disease* (*AD*) already had been partially dealt with. However, very recently a team of researchers at the University of Warwick's School of Engineering, UK, experts in trace metals analysis, high-resolution imaging, and neurodegenerative disorders have revealed that brain metals may drive disease progression (Everett et al. 2018).

In brains affected by Alzheimer's, researchers using nanoscale synchrotron X-ray speciation of iron and calcium compounds in amyloid plaque cores have identified chemically reduced iron species, with mineral forms including a magnetic iron oxide, called *magnetite*. Iron is an essential element in the brain, so it is critical to understand how its management is affected in the Alzheimer's patients. Advanced X-ray techniques being used have delivered a step change in the level of information about iron chemistry in the amyloid plaques. The formation of these plaques is associated with toxicity which causes cell and tissue death, leading to mental deterioration in Alzheimer's patients. The UK researchers have identified that in brains affected by Alzheimer's, several chemically reduced iron species including a proliferation of a magnetic iron oxide called *magnetite* – which is not commonly found in the human brain – occur in the amyloid protein plaques. The team had previously shown that these minerals can form when iron and the amyloid protein interact with each other. The research team having extracted and analyzed amyloid plaque cores from two deceased patients who had a formal diagnosis of Alzheimer's found out detailed evidence that the processes referred to took place in the brains of individuals who had *Alzheimer's disease* (*AD*). Also, unique observations about the forms of calcium minerals present in the amyloid plaques were made.

The research team proposed that interactions between iron and amyloid plaque produce the chemically reduced iron species, including *magnetite* (an iron oxide, $FeFe_2O_4$, that contains both Fe forms, Fe^{2+} and Fe^{3+}), which may account for toxicity that contributes to the development and progression of Alzheimer's. Still according to the authors, there are 850,000 people with dementia in the UK, with numbers set to rise to over one million by 2025. This will soar to two million by 2051.

Worldwide, an estimated 35.6 million people already live with a form of this neurodegenerative disorder, and these numbers are on a staggering rise. The WHO has projected that the number of cases of dementia will double by 2030 (65.7 million) and triple by the year 2050 (115.4 million). Already in America, the most common type of dementia, the *Alzheimer's disease* (*AD*), is the sixth leading cause of death; one in three senior passes with this type of crippling memory loss (WHO, 2015). In Portugal the number of individuals suffering from Alzheimer is estimated at 100–120 thousand.

It is considered that *Alzheimer's disease* (*AD*) is the result of a complex combination of subtle genetic, lifestyle, and environmental factors that affect the brain over a lifetime. Scientists believe that Alzheimer's disease is not an acute condition, but rather the result of numerous damages that occur over the years. This slow, cumulative patterning helps to explain why most patients with Alzheimer's disease do not present with symptoms until over the age of 65.

Alzheimer's disease (*AD*) is a common neurodegenerative disorder characterized by progressive loss of memory and cognitive function. With the accelerating population aging process, the prevalence of AD is estimated to rise steadily. Several studies indicate that osteoporosis and AD often coexist in elderly population and that osteoporosis is often unrecognized in AD patients until a fracture occurs. The associations between osteoporosis/BMD and AD had drawn increasing scientific interest, but the results were inconsistent. Some studies suggested that AD patients had lower BMD than controls, while others showed no significant differences.

Measuring bone mineral density (BMD) has been suggested as a method of identifying individuals at high risk of osteoporosis and fracture (Edwards et al. 2013). With the accelerating aging process, the prevalence of AD surely will steadily increase (Alzheimer's Association 2015). The associations between osteoporosis/BMD and AD had drawn increasing scientific interest, but the results being achieved have been inconsistent.

Very recently Lv et al. 2018, had systematically reviewed the current evidences on the association referred to. The authors conclude that there is an association between osteoporosis/BMD and AD. AD patients are at higher risk for osteoporosis and have lower BMD than controls, while osteoporosis and lower femoral neck BMD are also associated with a higher risk of AD. The risk of AD in osteoporosis patients and the risk of osteoporosis/BMD in AD patients are two different aspects to explore the connections between these two disorders. It is therefore impossible to rule out causality as an alternative explanation. A result of disease development may be the answer rather than being causal. More research with better design will be needed to address the issue.

Lithium salts have been used for centuries as a popular health tonic and have been applied to heal ailments as wide ranging as asthma, gout, and migraines. Studies carried out on a significant number of cases occurred in certain areas of the USA, Austria, England, Greece, and Japan have indicated that the lithium concentration levels in drinking waters show a general positive association between high lithium levels and beneficial behavioral, legal, and medical outcomes (Dawson, 1970; Schrauzer and Shrestha, 1990; Kapusta et al. 2011 Kabacs et al. 2011; Giotakos et al. 2015; and Sugawara et al. 2013). In the rare negative outcomes, lithium concentration levels were likely too low to yield any significant health effects (Mauer et al. 2014).

Pathologically Alzheimer's disease (AD) is being considered the result of two trademark injuries or lesions that occur at the cellular level: plaques and tangles. Plaques are formed by deposits of small protein fragments called amyloid-B or beta-amyloid peptides. Clumps of these proteins block the synapses or spaces between brain cells or neurons.

Lithium ions (at both high and low concentrations) have been shown to modify key cellular cascades that increase neuronal viability and resilience. Most prominently, lithium disrupts the key enzyme responsible for the development of the amyloid plaques and neurofibrillary tangles associated with Alzheimer's disease. This enzyme is called glycogen synthase kinase-3 (GSK-3) – a serine/threonine protein kinase that normally plays a major role in neural growth and development. In the healthy brain, GSK-3 is very important; it helps to carry out the synaptic remodeling that drives memory formation.

Very recently Greenblatt 2018 in the book *Integrative Medicine for Alzheimer's: The Breakthrough Natural Treatment Plan That Prevents Alzheimer's Using Nutritional Lithium* reveals that hope has come from new research showing the answer lies with an integrative approach, of which nutrition is a key factor. The key lies in low-dose nutritional lithium, a naturally occurring mineral with a long and well-documented history of restoring brain and nervous system function at the molecular level. Integrative medicine for Alzheimer's presents this simple and effective approach to the prevention and treatment of dementia, delivering a wealth of scientific support for the clinical use of nutritional lithium.

7.6.3 Other Adverse Effects of Clay and Clay Minerals

About both potential and effective pathogenicity, Carretero et al. 2013, state that clay minerals could be dangerous to human health through ingestion (an ancestral practice), inhalation, or dermal absorption due to the following factors: small particle size, reactive particle surfaces, limited solubility on the lungs, and fibrous crystal habit (in the case of *sepiolite* and *palygorskite*).

Clays and clay minerals could, in some cases, be dangerous when ingested. Clay eating may cause serious health risks, such as constipation and blockage of the lower intestine, which can only be remedied by surgery (Padilla and Torre 2006), reducing or impeding the release of potentially toxic natural chemical elements and/or compounds contained in the clay.

The identification, releasing mechanisms, and health effects of potentially toxic elements in clays and healing muds are dealt in various articles produced by Mascolo et al. 1999, 2004; Tateo et al. 2001, 2006, 2009; Vreca and Dolenec 2005; Kikouama et al. 2009a, b; and Gerencser et al. 2010.

Clays and clay minerals could be harmful also by inhalation and dermal absorption. Investigations on the pathogenicity by inhalation of *kaolinite*, talc, *sepiolite*, *palygorskite*, *illite*, and *montmorillonite* have been carried out.

Regarding inhalation, interesting information has been produced by Bignon 1990; Hollinger 1990; Guthrie 1992; Davis 1993; Ross et al. 1993; Santaren and Alvarez 1994; Governa et al. 1995; Galán 1996; Wagner et al. 1998; and Jurinski and Rimstidt 2001. However, the results of these investigations have been contradictory; some indicate that health risks only occur when the exposure time was very long, while others indicate that health risks could be caused by minerals such as quartz or asbestos associated with the clay.

Wagner et al. 1998, produced the Chap. 7 entitled "Clay Minerals and Health" of a book on *Environmental Interactions of Clays*, edited by Springer-Verlag. According to the authors, the health of humans can only be compromised by clay minerals which have been pulverized and dried, and the respiratory organs are affected only when the amount of dust produced is excessive. Also, the human lungs have produced mechanisms able to cope with the relatively small amounts of mineral dusts which are currently found in rural and most urban atmospheres. It is only when these mechanisms become overwhelmed, in terms of quantity and toxicity of the dust, that damage could occur.

The World Health Organization (WHO) in 2005 produced a report within the IPCS (International Programme on Chemical Safety), the "Environmental Health Criteria 231," report that examines the health effects of exposure to *bentonite*, *kaolin*, and selected clay minerals. Despite the ubiquitous exposure of the general population to low concentrations of *montmorillonite* and *kaolinite*, the main components of bentonite and *kaolin*, respectively, and other clay minerals, no data are available on its effects.

Long-term occupational exposure to bentonite dust may cause structural and functional damage to the lungs, but currently available data do not conclusively establish a dose-response or even a cause-and-effect relationship.

Long-term exposure to kaolin causes radiologically diagnosed pneumoconiosis, but clear-cut deterioration of respiratory function and related symptoms occur only in cases with prominent radiological findings. In this respect, the composition of the non-kaolinite constituents of the clay, as is the case of crystalline quartz, is much important.

Bentonite, kaolin, and other clays often contain *quartz*, exposure to which is causally related to silicosis and lung cancer as well as to statistically significant increases in the incidence of or mortality from chronic bronchitis and pulmonary emphysema. The extensive use of *bentonite* or *kaolin* in cosmetics has not been found to produce local or systemic adverse effects. Tests have also revealed that *bentonite* and *kaolin* have low toxicity to a wide variety of aquatic species.

The biological effects of clay minerals result from not only their composition but also their particle size. In this respect, the decreasing rank order of *quartz*, *kaolinite*, and *montmorillonite* to damage lung tissue is consistent with their known relative active surface areas and surface chemistries.

Maxim et al. 2016, in an article titled “Bentonite toxicology and epidemiology: A review,” state that *bentonite* is not classified as a carcinogen by any regulatory or advisory entities. However, some *bentonite* may contain variable amounts of respirable crystalline silica which is recognized human carcinogen.

Before finalizing the chapter their authors consider that although not in-text cited, commented and discussed due to chapter and book extension limitations, along the chapter preparation process a significant number of scientific papers had been consulted which could call the interest of potential readers, as is the case of the following references: Abrahams (2002), Aguzzi et al. (2006), Antonelli and Donelli (2018), Armijo (2015), Armijo and Armijo (2006), Arribas et al. (2010a), Arribas et al. (2010b), Artymuk et al. (2010), Awad et al. (2017), Baby et al. (2004), Bagnato (2004), Bagnato et al. (2004), Balogh et al. (2005), Banenzoue et al. (2014), Barhoumi et al. (2019), Barros et al. (2010), Bech (1987), Beer et al. (2013), Belkaide and Hand (2014), Bellometti et al. (1997), Bellometti et al. (2000), Bellometti et al. (2005), Bender et al. (2005), Benedetti et al. (2007), Branco et al. (2016), Bui QC et al. (2016), Caflisch et al. (2018), Cantarini et al. (2007), Cao et al. (1982), Cara et al. (2000), Carazo et al. (2018), Carbajo and Maraver (2015), Carbajo and Maraver (2016), Carbajo et al. (2010), Carretero (2013), Carretero (2020a), Carretero (2020b), Carretero et al. (2014), Casas et al. (2013), Cavalcanti et al. (2016), Ceccarelli et al. (2010), Ceruti et al. (2003), Charrié (2007), Cho and Blaser (2012), Codish et al. (2005a), Codish et al. (2005b), Cozzi et al. (2004), Curini et al. (1990), Davey et al. (2007), Dawson et al. (1970), De Michele et al. (2008), De Vos (2010), Denaverre (1975), Deribe et al. (2015c), Edraki and Zaarei (2018), Elkayam et al. (2000), Espírito Santo et al. (2011), European Pharmacopeia

(7th edition) (2011), European Spas Association (ESA) (2006), Fahlén et al. (2012), Faílde and Mosquera (2006), Khurama et al. (2014), Kikouama et al. (2009b), Kostyniak et al. (2003), Lafi and Al-Dulaimy (2011), Legido and Mourelle (2008), Legido et al. (2007), Lewis (1935), Li et al. (2009), Lopez-Galindo and Viseras (2004), Lopez-Galindo et al. (2007), Macheka et al. (2016), Magana and Quintana (2008), Mahboob et al. (2009), Malachová et al. (2011), Maraver (2008), Massaro et al. (2018a), Massaro et al. (2018b), Matz et al. (2003), McInnes (2012), Meijide et al. (2010), Metge et al. (2007), Michele et al. (2006), Mihranyan et al. (2012), Mishra et al. (2017), Munñoz et al. (2015), Ngole et al. (2010), Nkansah et al. (2016), Nnorom (2016), Novelli (1996), Novelli (1998), Novelli (2000), O'Neill (2016), Odabasi et al. (2009), Odangowei and Okiemute (2015), Onnainty et al. (2016), Otto et al. (2016), Panico and Imperato (2009), Pedersen et al. (2000), Pena-Ferreira et al. (2010a), Pena-Ferreira et al. (2010b), Pena-Ferreira et al. (2011), Photo-Jones et al. (2015), Pozo (2015), Pozo et al. (2013), Price (1977), Rambaud (1989), Rambaud et al. (1986), Reichardt (2008), Reinbacher (2003), Rondanelli et al. (2012), San Martin Bacaicoa (1994), Sandri et al. (2014), Sandri et al. (2016), Sandri et al. (2017), Santos et al. (2014), Sawai (2003), Schaefer and Redelmeir (1996), Schmidt-Malan et al. (2018), Schnetz and Fartasch (2002), Schruazer and Shrestha (1990), Serofilli (1994), Silva et al. (2015), Soria et al. (2018), Steinstand (2012), Stokes (2006), Suresh et al. (2010), Tenti et al. (2014), Turpin (2004), Ubogui et al. (1991), Ubogui et al. (1998), Untura et al. (2007), Unuabonah and Taubert (2014), Unuabonaha et al. (2018), Vaht et al. (2008), Varga (2010), Velasco et al. (2016), Veniale (1999), Veniale (2007), Vergaro et al. (2012), Vermeer (1986), Vincevica-Gaile and Stankevica (2018), Viseras et al. (2006), Viseras et al. (2008), Viseras et al. (2010), Viseras et al. (2015), Welsh (2011), WHO (2005), Wigler et al. (1995), Wilkinson and Moore (1982), Williams (2011), Williams and Haydel (2010), Worrall (1975), Woywodt and Kiss (1999), Yuan et al. (2015), Yvon and Ferrand (1996), Zague et al. (2008), Zarate-Reyes et al. (2017a), Zarate-Reyes et al. (2017b).

References

Abdullayev E, Lvov Y (2016) Halloysite for controllable loading and release. Developments in clay science, vol 7. Elsevier, pp 554–605

Abrahams PW (1997) Geophagy (soil consumption) and iron supplementation in Uganda. Tropical Med Int Health 2:617–623

Abrahams PW (2002) Soils: their implications to human health. Sci Total Environ 291:1–32

Abrahams PW (2005) Geophagy and the involuntary ingestion of soils. In: Selinus O, Alloway B, Centeno JA, Finkelman RB, Fuge R, Lindh U, Smedley P (eds) Essentials of medical geology. Elsevier Academic, pp 435–458

Abrahams PW (2010) Chapter 23: Earth eaters: ancient and modern perspectives on human geophagy. In: Landa ER, Feller C (eds) Soil and culture. Springer, Dordrecht, pp 369–398

Abrahams PW (2012) Involuntary soil ingestion and geophagia: a source and sink of mineral nutrients and potentially harmful elements to consumers of earth materials. Appl Geochem 27:954–968

Abrahams PW (2013) Geophagy and the involuntary ingestion of soil. In: Selinus O, Alloway B, Centeno JA, Finkelman RB, Fuge R, Lindh U, Smedley P (eds) Essentials of medical geology: revised edition. Springer, Dordrecht, pp 433–454

Abrahams PW, Parsons JA (1996) Geophagy in the tropics: a literature review. Geogr J 162:63–72

Abrahams PW, Follansbee MH, Hunt A, Smith B, Wragg J (2006) Iron nutrition and possible lead toxicity: an appraisal of geophagy undertaken by pregnant women of UK Asian communities. Appl Geochem 21:98–108

Abrahams PW, Davies TC, Solomon AD, Trow AJ, Wragg J (2013) Human geophagia, calabash chalk and undongo: mineral element nutritional implications. PLoS One 8(1). https://doi.org/10.1371/journal.pone.0053304

Abu-Shakra M, Mayer A, Friger M, Harari M (2014) Dead Sea mud packs for chronic low back pain. Isr Med Assoc J 16:574–577

Adusumilli S, Haydel SE (2016) In vitro antibacterial activity and in vivo efficacy of hydrated clays on Mycobacterium ulcerans growth. BMC Complement Altern Med 16(40):1–9. https://doi.org/10.1186/s12906-016-1020-5

Aguzzi C, Cerezo P, Viseras C, Caramella C (2006) Use of clays as drug delivery systems: possibilities and limitations. Appl Clay Sci 36:22–36

Aguzzi C, Sandri G, Cerezo P, Carazo E, Viseras C (2016) Health and medical applications of tubular clay minerals. Developments in Clay Science, vol 7, Chapter 26, 708–725, Elsevier Ltd

Al-Ghazzewi FH, Tester RF (2014) Impact of prebiotics and probiotics on skin health. Benefic Microbes 5:99–107

Al-Rmalli SW, Jenkins RO, Watts MJ, Haris PI (2010) Risk of human exposure to arsenic and other toxic elements from geophagy: trace element analysis of baked clay using inductively coupled plasma mass spectrometry. Environ Health 9(79) http://www.ehjournal.net/content/9/1/79

Alzheimer's Association (2015) Alzheimer's disease: facts and figures. Alzheimers Dement 11(3):332–384

Amin K, Riddle CC, Aires DJ, Achweiger ES (2007) Common and alternate oral antibiotic therapies for acne vulgaris: a review. J Drugs Dermatol 6(9):873–880

An N, Zhou X, Tong D, Yu W (2015) Immobilization of enzymes on clay minerals for biocatalysts and biosensors. Appl Clay Sci 114:283–296

Andreoli C, Rascio N (1975) The algal flora in the thermal baths of Montegrotto Terme (Padua): its distribution over one-year period. Int Rev Ges Hydrobiol 60:857–871

Antonelli M, Donelli D (2018) Int J Biometeorol, Springer. https://doi.org/10.1007/s00484-018-1599-y

Antonelli M, Donelli D, Fioravanti A (2018) Effects of balneotherapy and spa therapy on quality of life of patients with knee osteoarthritis: a systematic review and meta-analysis. Rheumatol Int 38(10):1807–1824

Araújo ARTS, Paiva T, Ribeiro MP, Coutinho P (2015) Chapter 11: Innovation in Thermalism: An example in Beira interior region of Portugal. In: Peris-Ortiz M, Álvarez-Garcia J (eds) Health and wellness tourism: emergence of a new market segment. Springer, pp 165–180

Argenziano G, Delfino M, Russo N (2004) Mud and bath therapy in the acne cure. Clin Ter 155(4):121–125

Arias CA, Murray BE (2009) Antibiotic-resistant bugs in the 21st century: a clinical super-challenge. New Engl J Med 360:439–443

Armijo F (1991) Propiedades térmicas de los peloides. Bol Soc Esp Hidrol Med 6(3):151–158

Armijo F (2015) Fases sólidas de los peloides: Propiedades térmicas y mecânicas. Balnea 10:143–162

Armijo F, Armijo O (2006) Curva de enfriamiento de los peloides españoles. An Hidrol Med 1:97–110

Armijo F, Carbajo JM, Fernandez-Toran MA, Corvillo I, Vazquez I, Carretero MI, Maraver F (2014) Thermal profile of three clays suitable to be used as solid components in the preparation of peloids. Appl Clay Sci 99:131–143

Armijo F, Maraver F, Pozo M, Carretero MI, Armijo O, Fernández-Toran MA, Fernández-González MV, Corvillo I (2016) Thermal behaviour of clays and clay-water mixtures for pelotherapy. Appl Clay Sci 126:50–56

Arribas M, Meijide R, Mourelle ML (2010a) Evolución de la psoriasis tratada con peloides y água mineromedicinal de La Toja. In: Maraver F, Carretero MI (eds) Libro de Resúmenes del II Congreso Iberoamericano de Peloides. C.E.R.S-A, Madrid, p 75

Arribas M, Meijide R, Mourelle ML, Gómez CP, Legido JL (2010b) Projecto de innovación para el desarrollo de un peloide termal para el balneario isla de la Toja. In: Maraver F, Carretero MI (eds) Libro de Resúmenes del II Congreso Iberoamericano de Peloides. C.E.R.S-A, Madrid, p 76

Artymuk NV, Kira EF, Kondratieva TA (2010) Intravaginal gel prepared from Dead Sea peloid for treating luteal-phase defect. Int J Gynaecol Obstet 108(1):72–73

Aufreiter S, Hancock RG, Mahaney WC, Stamolic-Robb A, Sanmugadas K (1997) Geochemistry and mineralogy of soils eaten by humans. Int J Food Sci Nutr 48:293–305

Awad ME, López-Galindo A, Setti M, El-Rahmany MM, Viseras C (2017) Kaolinite in pharmaceuticals and biomedicine. Int J Pharm 533:34–48

Baby AR, Zague V, Maciel CPM, Salgado-Santos KY, Arêas EPG, Kaneko TM, Consiglieri VO, Velasco MVR (2004) Development of cosmetic mask formulations. Braz J Pharm Sci 40(1):159–161

Bagnato G (2004) Clinical improvement and serum amino acid levels after mud-bath therapy. Int J Clin Pharmacol Res 24:39–47

Bagnato G, De Filippis LG, Morgante S, Morgante ML, Farina G, Caliri A, Romano C, DÁvola G, Pinelli P, Calpona PR, Streva P, Resta ML, De Luca G, Di Giorgio R (2004) Clinical improvement and serum amino acid levels after mud-bath therapy. Int J Clin Pharmacol Res 24(2–3):39–47

Balogh Z, Ordögh J, Gász A, Német L, Bender T (2005) Effectiveness of balneotherapy in chronic low back pain: a randomized single-blind controlled follow-up study. Forsch Komplementarmed Klass Naturheilkd 12(4):196–201. https://doi.org/10.1159/000086305

Banenzoue C, Signing P, Mbey JA, Njopwouo D (2014) Antacid power and their enhancements in some edible clays consumed by geophagia in Cameron. J Chem Pharm Res 6(10):668–676

Barhoumi T, Bekri-Abbes I, Srasra E (2019) Physicochemical characteristics and suitability of curative pastes of Tunisian clay minerals and termal waters for use in pelotherapy. C R Chim 22(2–3):126–131

Barros M, Santos D, Pena Ferreira MR, Silva JBP, Amaral MH, Sousa Lobo JM, Gomes JHCA, Gomes CSF (2010) Estudos de pré-formulação de um pelóide anticelulitico com argila esmectítica da ilha do Porto Santo. In: Maraver F, Carretero MI (eds) Libro de Resúmenes del II Congreso Iberoamericano de Peloides. C.E.R.S-A, Madrid, pp 77–78

Baschini MT, Pettinari GR, Vallés JM, Aguzzi C, Cerezo P, López-Galindo A, Setti M, Viseras C (2010) Suitability of natural Sulphur-rich muds from Copahue (Argentina) for use as semisolid health care products. Appl Clay Sci 49:205–212

Baschini MT, Piovano E, López-Galindo A, Dietrich D, Setti M (2014) Composición y propriedades de fangos (peloides), águas y sales procedentes de lagunas y lagos salinos usados com fines terapêuticos y cosméticos. In: Peloteraia: Aplicaciones médicas y cosméticas de fangos termales. Torres HA (coordenador), Fundación Bibilis, 145–154

Baschini MT, Soria C, Pettinari G, Gamboa E, Sánchez M, Jalil ME (2018) Chapter 2: Fangos de Copahue: Una Vision desde la Ciencia. In: Soria CO, Vela ML, Jalil ME (eds) Copahue: La Ciencia, Lo Magico y El Arte de Curar. Repositorio del Libro, Universidad Nacional de Comahue, Argentine, pp 25–47. 170pp

Bech J (1987) Les terres médicinales. Discurs per Reial Académia de Farmácia de Barcelona. Reial Académia de Farmácia de Barcelona-CIRIT (Generalitat de Catalunya), Barcelona

Beck MA (2006) Selenium and viral infections. In: Hatfield DL, Berry MJ, Gladyshev VN (eds) Selenium. Springer, Boston

Beck MA, Handy J, Levander OA (2004) Host nutriviral status: the neglected virulence factor. Trends Microbiol 12(9):417–423

Beer AM, Grozeva A, Sagorchev P, Lukanov J (2003a) Comparative study of the thermal properties of mud and peat solutions applied in clinical practices. Biomed Tech (Berl) 48:301–305

Beer AM, Junginger HE, Lukanov J, Sagorchev P (2003b) Evaluation of the permeation of peat substances through human skin in vitro. Int J Pharm 253:169–175

Beer AM, Fetaj S, Lange U (2013) Peloid therapy: An overview of the empirical status and evidence of mud therapy. Z Rheumatol (Apr 11)

Behroozian S, Svensson SL, Davies J (2016) Kisameet clay exhibits potent antibacterial activity against the ESKAPE pathogens. Am Soc Microbiol, mBios 7(1):e01842–e01815

Belkaide Y, Hand T (2014) Role of the microbiota in immunity and inflammation. Cell 157(1):121–141

Belkaide Y, Segre JA (2014) Dialogue between skin microbiota and immunity. Science 346:954–959

Bellometti S, Cecchettin M, Galzigna L (1997) Mud pack therapy in osteoarthrosis. Changes in serum levels of chondrocyte markers. Clin Chim Acta 268(1–2):101–106

Bellometti S, Poletto M, Gregotti C, Richelmi P, Bertè F (2000) Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients. Int J Clin Pharmacol Res 20(3–4):69–80

Bellometti S, Richelmi P, Tassoni T, Bertè F (2005) Production of matrix metalloproteinases and their inhibitors in osteoarthritic patients undergoing mud bath therapy. Int J Clin Pharmacol Res 25(2):77–94

Bellometti S, Gallotti C, Pacileo G, Rota A, Tenconi MT (2007) Evaluation of outcomes in spa-treated osteoarthrosic patients. J Prev Med Hyg 48(1):1–4

Bender T, Karagülle Z, Bálint G, Gutenbrunner C, Bálint P, Sukenik S (2005) Hydrotherapy, balneotherapy, and spa treatment in pain management. Rheumatol Int 25:220–224

Benedetti S, Pagliarani S, Benvenuti F, Marini D, Galli T, Oliva F, Lazzari P, Canestrari F (2007) Antioxidative effects of sulphurous water from Macerata Feltria thermal resort in patients with osteoarthritis. Prog Nutr 9(1):46–52

Bignon J (1990) Health related effects of phyllosilicates. In: Bignon J (ed) NATO ASI series, vol G21. Springer, Berlin/Heidelberg

Bolzinger MA, Briançon S, Pelletier J, Chevalier Y (2012) Penetration of drugs through skin, a complex rate-controlling membrane. Curr Opin Colloid Interface Sci 17(3):156–165

Bonglaisin JN, Mbofung CMF, Lantum DN (2011) Intake of lead, cadmium and mercury in kaolin-eating: a quality control. J Med Sci 11(7):267–273

Branco M, Rego NN, Silva PH, Archanjo IE, Ribeiro MC, Trevisani VF (2016) Bath thermal waters in the treatment of knee osteoarthritis: a randomized controlled clinical trial. Eur J Phys Rehab Med 52(4):422–430

Brand CE, de Jager L, Ekosse GE (2010) Possible health effects associated with human geophagic practice: an overview. SA Med Technol 23(1):11–13

Brevik EC (2013) Climate change, soils and human health. In: Brevik EC, Burgess LC (eds) Soils and human health. CRC Press, Boca Raton, pp 345–383

Browman DL (2004) Tierras comestibles de la Cuenca del Titicaca: Geofagia en la prehistoria boliviana. Estudios Atacameños 28:133–141

Brunet de Courssou L (2002) 5th WHO advisory group meeting on Buruli ulcer, Study Group Report on Buruli Ulcer Treatment with Clay, Geneva, Switzerland

Buck BJ, Londono SC, McLaurin BT, Metcalf R, Mouri H, Selinus O, Shelembe R (2016) The emerging field of medical geology in brief: some examples. Environ Earth Sci 75:449. https://doi.org/10.1007/s12665-016-5362-6

Bui Qc NHC, Vesentsev AI, Buhanov VD, Sokolovsky PV, Mihaylyukova MO (2016) The antibacterial properties of modified bentonite deposit *tam bo* in Vietnam. Research result: pharmacology and clinical. Pharmacology 2(3):63–74

Bujdáková H, Bujdáková V, Májekcvá-Koščová H, Gaálová B, Bizovská H, Bohác P (2018) Antimicrobial activity of organoclays based on quaternary alkylammonium and alkylphosphonium surfactants and montmorillonite. Appl Clay Sci 158:21–28

Burguera EF, Vela-Anero A, Magalhães J (2012) Effect of hydrogen sulfide sources on inflammation and catabolic markers on interleukin 1β-stimulated human articular chondrocytes. Osteoarthr Cartil 22:1026–1035

Caflisch KM, Schmidt-Malan SM, Mandrekar JN, Karau MJ, Nicklas JP, Williams LB, Patel R (2018) Antibacterial activity of reduced iron clay against pathogenic bacteria associated with wound infections. Int J Antibacterial Agents 52:1–5

Cantaluppi C, Fasson A, Ceccotto F, Cianchi A, Degetto S (2014) Radionuclides concentration in water and mud of Euganean thermal district. Int J Environ Res 8:237–248

Cantarini L, Leo G, Giannitti C, Cevenini G, Barberini P, Fioravanti A (2007) Therapeutic effect of spa therapy and short wave therapy in knee osteoarthritis: a randomized, single blind, controlled trial. Rheumatol Int 27:523–529

Cao HC, Lou ZY, Qu FR et al (1982) Prevention of Keshan disease and influence of abnormal heart by using sodium selenite. Chinese J Endemiol 1(3):150–154

Cao J, Li S, Shi Z, Yue Y, Sun J, Fu Q (2008) Articular cartilage metabolism in patients with Kashin–Beck disease: An endemic osteoarthropathy in China. Osteoarthr Cartil 16(6):680–688

Cara S, Carcangiu G, Padalino G, Palomba M, Tamanini M (2000) The bentonites in pelotherapy: thermal properties of clay pastes from Sardinia (Italy). Appl Clay Sci 16:125–132

Carabelli A, De Bernardi Valserra G, De Bernardi Valserra M, Tripoli S, Belloti E, Pozzi R, Campiglia C, Arcangeli P (1998) Effect of termal mud baths on normal, dry and seborrheic skin. Clin Ter 194(4):271–275

Carazo E, Borrego-Sánchez A, García-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C, Viseras C (2018) Advanced inorganic nanosystems for skin drug delivery. Chem Rec:891–899. https://doi.org/10.1002/tcr.201700061

Carbajo JM, Maraver F (2015) Hydrogen sulfide and health. New insights Balnea 10:93–105

Carbajo JM, Maraver F (2016) Absorção cutânea de sulfureto de hidrogénio. Revista Factores de Risco 41(Jul-Set):54–62

Carbajo JM, López-Delgado MI, Armijo F, Maraver F (2010) Skin response to osmotic cosmetics elaborated with mud made from chlorided ferruginous mineral water. Presse Therm Clim 147:153–154

Cardoso-Gomes J, Gomes CSF (2015) Mud used for therapeutic and skin care purposes at the beach of Porto de Mós, Algarve, Portugal. Balnea 10:355–356

Carretero MI (2002) Clay minerals and their beneficial effects upon human health: a review. Appl Clay Sci 21(3–4):155–163

Carretero MI (2013) Metodologia aplicada a la determinación del peloid óptimo. Livro de Actas do III Congresso Iberoamericano de Peloides. Nunes J, Gomes C, Silva J. (eds), Ponta Delgada, São Miguel, Açores, 19–24

Carretero MI (2020a) Clays in Pelotherapy: a review, part I – mineralogy, chemistry, physical and physicochemical properties. Applied Clay Science 189. https://doi.org/10.1016/j.clay.2020.105526

Carretero MI (2020b) Clays in Pelotherapy: a review, part II – organic compounds, microbiology and medical application. Appl Clay Sci 189. https://doi.org/10.1016/j.clay.2020.105531

Carretero MI, Pozo M (2007) Mineralogía aplicada: Salud y medio ambiente. Thomson, Madrid, 464 pp

Carretero MI, Gomes CSF, Tateo F (2006) Clays and human health. In: Bergaya F, BKG T, Lagaly G (eds) Handbook of clay science, Developments in clay science, vol 1. Elsevier (The Netherlands), pp 717–741

Carretero MI, Pozo M, Martin-Rubi JA, Pozo E, Maraver F (2010) Mobility of elements in interaction between artificial sweat and peloids used in Spanish spa. Appl Clay Sci 48(3):506–515

Carretero MI, Gomes CSF, Tateo F (2013) Chapter 5: Clays, drugs and human health. In: Bergaya F, Lagaly G (eds) Handbook of clay science, vol 5, 2nd edn. Part B. Techniques and Applications. Elsevier (The Netherlands), pp 711–764

Carretero MI, Pozo M, Legido JL, Fernandez-González MV, Delgado R, Gómez I, Armijo F, Maraver F (2014) Assessment of three Spanish clays for their use in pelotherapy. Appl Clay Sci 99:131–143

Casas LM, Pozo M, Gómez CP, Pozo E, Bessieres D, Plantier F, Legido JL (2013) Thermal behaviour of mixtures of bentonitic clay with different salinity waters. Appl Clay Sci 72:18–25

Cavalcanti RKBC, Ferreira HS, Macedo RO (2016) Caracterização fisico-química de argilas bentoníticas para uso em maquiagem mineral. 60° Congresso Brasileiro de Cerâmica 15 a 18 de maio de 2016, Águas de Lindóia, SP, 51–66

Ceccarelli F, Perricone C, Alessandri C, Modesti M, Lagnocco A, Croia C, Di Franco M, Valesini G (2010) Exploratory data analysis on the effects of non-pharmacological treatment for knee osteoarthritis. Clin Exp Rheumatol 28:250–253

Centini M, Tredici MR, Biondi N, Buonocore A, Maffei Facino R, Anselmi C (2015) Thermal mud maturation: organic matter and biological activity. Int J Cosmet Sci 37:339–347

Ceruti PO, Fey M, Pooley J (2003) Soil nutrient deficiencies in an area of endemic osteoarthritis (Mseleni joint disease) and dwarfism in Maputaland, South Africa. In: Geology and health: closing the gap. Oxford University Press, New York, pp 151–154

Charrié JC (2007) ABC de l'argile. Grancher éd., 238pp, ISBN 2-7339-1003-5

Chen J (2012) An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). Asia Pac J Clin Nutr 21(3):320–326

Chen X, Yang G, Chen J, Chen X, Wen Z, Ge K (1980) Studies on the relations of selenium and Keshan disease. Biol Trace Elem Res 2:91–107

Cho I, Blaser MJ (2012) The human microbiome at the interface of health and disease. Nat Rev Genet 13:260–270

Codish S, Abu-Shakra M, Flusser D, Friger M, Sukenik S (2005a) Mud compress therapy for the hands of patients with rheumatoid arthritis. Rheumatol Int 25:49–54

Codish S, Dobrovinsky S, Abu-Shakra M, Flusser D, Sukenik S (2005b) Spa therapy for ankylosing spondylitis at the Dead Sea. Isr Med Assoc J 7:443–446

Costantino M (2006) Sulphur mud-bath treatment in osteoarthrosis: therapeutic activity and efficiency on the quality of life. Clin Ter 157:525–529

Costantino M, Lampa E (2005) Psoriasis and mud bath therapy: clinical-experimental study. Clin Ter 156:145–149

Cozzi F, Carrara M, Sfriso P, Todesco S, Cima L (2004) Anti-inflammatory effect of mud-bath applications on adjuvant arthritis in rats. Clin Exp Rheumatol 22:763–766

Crivelli PE (1986) Non-filarial elephantiasis in Nyambene range: a geochemical disease. East Afr Med J 63(3):191–194

Cunningham TB, Koehl JL, Summers JS, Haydel SE (2010) pH-dependent metal ion toxicity influences of the antibacterial activity of two natural mineral mixtures. PLoS One 5:e9456

Curini R, D'Ascenzo G, Fraioli A, Lagana A, Marino A, Messina B (1990) Instrumental multiparametric study of the maturing of therapeutic muds of some Italian spas. Thermochim Acta 157:377–393

Curri SB, Bombardelli E, Grossi F (1997) Observations on organic components of thermal mud: Morphohistochemical and biochemical studies on lipid components of mud of the Terme Dei Papi (Laghetto del Bagnaccio, Viterbo), Chemical bases of the interpretation of biological and therapeutic actions of thermal mud. Clin Ter 148:637–654

Da Silva PSC, Torrecilha JK, Gouvea PFM, Máduar MF, de Oliveira SMB, Scapin MA (2015) Chemical and radiological characterization of Peruíbe black mud. Appl Clay Sci 118:221–230

Dai T, Tanaka M, Huang Y-Y, Hamblin M (2011) Expert Rev Anti-Infect Ther 9(7):857–879

Danford DE (1982) Pica and nutrition. Annu Rev Nutr 2:303–322

Dário GMI, Da Silva GG, Gonçalves DL, Silveira P, Junior AT, Angioletto E, Bernardin AM (2014) Evaluation of the healing activity of therapeutic clay in rat skin wounds. Mater Sci Eng C 43:109–116

Dashiff A, Junka RA, Libera M, Kadouri DE (2011) Predation of human pathogens by the predatory bacteria *Micavibrio aeruginosavorus* and *Bdellovibrio bacteriovorus*. J Appl Microbiol 110(2):431–444

Davey G, Tekola F, Newport MJ (2007) Podoconiosis: non-infectious geochemical elephantiasis. Intensive Crit Care Nurs 101:1175–1180

David R (2012) Antimicrobials: why zinc is bad for bacteria. Nat Rev Microbiol 10(1) 4pp

Davies TC (2008) Environmental health impacts of east African rift volcanism. Environ Geochem Health 30:325–338. https://doi.org/10.1007/s10653-008-9168-7

Davies TC (2010) Chapter 8: Medical geology in Africa. In: Selinus O, Finkelman RB, Centeno J (eds) Medical geology – a regional synthesis, 1st edn. Springer, Amsterdam, pp 199–219

Davies TC, Mundlano HR (2010) Environmental health impacts of dispersed mineralization in South Africa. J Afr Earth Sci 58(4):652–666

Davies TC, Lar UA, Solomon AO, Abraham PW (2008) Mineralogy and geochemistry of geophagic materials consumed in Jos-Plateau State of Nigeria. Paper presentation at International Conference South Africa

Davis JMG (1993) *In vivo* assays to evaluate the pathogenic effects of minerals in rodents. In: Guthrie GD, Mossman BT (eds) Health effects of mineral dusts, reviews in mineralogy, vol 28. Mineralogical Society of America, Washington, DC, pp 471–487

Dawson EP, Moore TD, McGranity WJ (1970) The mathematical relationship of drinking water lithium and rainfall on mental hospital admission. Dis Nerv Syst 31:1–10

De la Rosa-Gomez I, Olguín MT, Garcia-Sosa I, Alcantara D, Rodriguez-Fuentes G (2008) Silver supported on natural Mexican zeolite as an antibacterial material. Micropor Mesopor Mater 39:431–444. https://doi.org/10.1016/S1387-1811(00)00217-1

De Michele D, Giacomino M, Untura Filh M, Belderrain A (2008) Effectos sistémicos de los fangos minerales: Revisión de la Literature de los últimos 10 anos/Systemics effects of mineral muds: A ten years Literature review. Balnea 4:115–122

De Vos P (2010) European material medica in historical texts: longevity of a tradition and implications for future use. J Ethnopharmacol 176:10–17

Delfino M, Russo N, Migliaccio G, Carraturo N (2003) Experimental study on efficacy of thermal muds of Ischia Island combined with balneotherapy in the treatment of psoriasis vulgaris with plaques. Clin Ter 154(3):167–171

Demirci S, Ustaoglu Z, Yilmazer GA, Sahin F, Baç N (2014) Antimicrobial properties of zeolite-X, and zeolite-a ion exchanged with G, Cu, and Zn against a broad range of microorganisms. Appl Biochem Biotechnol 172:1652–1662

Denaverre M (1975) Face masks. In: Denaverre M (ed) The chemistry and manufacture of cosmetics - volume 3, 2nd edn. Continental Press, Orlando

Deribe K (2018) Podoconiosis today: challenges and opportunities. Trans R Soc Trop Med Hyg 112:473–475

Deribe K, Cano J, Newport MJ et al (2015a) Mapping and modelling the geographic distribution and the environmental limits of podoconiosis in Ethiopia. PLoS Negl Trop Dis 9:e0003946

Deribe K, Wanji S, Shafi O et al (2015b) The feasibility of eliminating podoconiosis. WHO Bull:712–718

Deribe K, Brooker S, Pullan R et al (2015c) Epidemiology and individual, household and geographical risk factors of podoconiosis. Am J Hyg Trop Med:148–158

Deribe K, Kebede B, Mengistu B, Negussie H, Sileshi M, Tamiru M, Tomczyk S, Tekola-Ayele F, Davey G, Fentaye A (2017) Podoconiosis in Ethiopia: from neglect to priority public health problem. Ethiop Med J 55(Suppl 1):65–74

Deribe K, Cano J, Trueba ML, Newport MJ, Davey G (2018) Global epidemiology of podoconiosis: a systematic review. PLoS Negl Trop Dis 12(3). https://doi.org/10.1371/journal.pntd.0006324

Detellier C, Schoonheydt RA (2014) From platy kaolinite to nanorolls. Elements 10:201–206

Díaz Rizo O, Rudnikas AG, López JOA, D'Alessandro Rodríguez K, González Hernández P, Castillo JRF, Blanco Padilla D (2013) Radioactivity levels and radiation hazard of healing mud from San Diego River, Cuba. J Radioanal Nucl Chem 295:1293–1297

Díaz Rizo O, Suárez Muñoz M, González Hernández P, Rudnikas AG, D'Alessandro Rodríguez K, Rodríguez CMM, JRF C, Martínez-Villegas NV, Zerquera JT (2018) Radioactivity levels in peloids used in main Cuban spas. J Radioanal Nucl Chem 316:95–99

Diekema DJ, BootsMiller BJ, Vaughn TE, Woolson RF, Yankey JW (2004) Antimicrobial resistance trends and outbreak frequency in United States hospitals. Clin Infect Dis 38:78–85

Dinkele ES, Ballo R, Fredlund V, Ramesar R, Gibbon V (2020) Mseleni joint disease: An endemic arthritis of unknown causes. Lancet Rheumatol 2(1). https://doi.org/10.1016/S2665-9913(19)30104-3

Domenici D (2019) Tasting clay, testing clay. Medicinal earths, Bucarophagy and experimental knowledge in Lorenzo Legati's Museo Cospiano (1677). Cromohs (Cyber Rev Mod Hist) 22:16. https://doi.org/10.13128/cromohs-11701

Dreno B (2004) Topical antibacterial therapy for *acne vulgaris*. Drugs 64(21):2389–2397

Dudare D, Klavins M (2013) Complex-forming properties of peat humic acids from a raised bog-profiles. J Geochem Exp 129:18–22

Edraki M, Zaarei D (2018) Modification of montmorillonite clay with 2-mercaptobenzimidazole and investigation of their antimicrobial properties. Asian J Green Chem 2:189–200

Edwards MH, Jameson K, Denison H et al (2013) Clinical risk factors, bone density and fall history in the prediction of incident fracture among men and women. Bone 52(2):541–547

Ekosse GE, Jumbam DN (2010) Geophagic clays: their mineralogy, chemistry and possible human health effects. Afr J Biotechnol 9(40):6755–6767

Ekosse GE, Ngole VM (2012) Mineralogy, geochemistry and provenance of geophagic soils from Swaziland. Appl Clay Sci 57:25–31

Elkayam O, Ophir J, Brener S, Paran D, Wigler I, Efron D, Even-Paz Z, Politi Y, Yaron M (2000) Immediate and delayed effects of treatment at the Dead Sea in patients with psoriatic arthritis. Rheumatol Int 19:77–82

EMA (European Medicines Agency), 2008) Guideline on the specification limits for residual metal catalysts for metal reagents. https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003586.pdf

Espejo-Antúnez L, Cardero-Durán MA, Garrido-Ardila EM, Torres-Piles S, Caro-Puértolas B (2013) Clinical effectiveness of mud pack therapy in knee osteoarthritis. Rheumatology (Oxford) 52:659–668

Espírito Santo C, Lam E, Elowsky C, Quaranta D, Domaille D, Chang C, Grass G (2011) Bacterial killing by dry metallic copper surfaces. Appl Environ Microbiol 77:794–802

European Pharmacopeia (7th edition) (2011) Directorate for the quality of medicines of the Council of Europe, Strasbourg, France

European Spas Association (ESA) (2006). Quality criteria of the European spas association (ESPA), 31p

Evcik D, Kavuncu V, Yeter A, Yigit I (2007) The efficacy of balneotherapy and mud-pack therapy in patients with knee osteoarthritis. Joint Bone Spine 74:60–65

Everett J, Collingwood JF, Tjendana-Tjhin V, Brooks J, Lermyte F, Plascencia-Villa G, Hands-Portman I, Dobson J, Perry G, Telling ND (2018) have produced a paper entitled "Nanoscale synchrotron X-ray speciation of iron and calcium compounds in amyloid plaque cores from Alzheimer's disease subjects. Nanoscale 2018. https://doi.org/10.1039/C7NR06794A

Fahlén A, Engstrand L, Baker BS, Powles A, Fry L (2012) Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res 304:15–22

Faílde RM, Mosquera LM (2006) Afecciones dermatológicas y cosmética dermotermal. Técnicas y Tecnologias en Hidrologia Médica y Hidroterapia:175–179

Fakhrullin R, Lvov YM (2016) Halloysite clay nanotubes for tissue engineering. Nanomedicine 11:2243–2246

Fakhrullina GI, Akhatova FS, Lvov YM, Fakhrullin RF (2015) Toxicity of halloysite clay nanotubes *in vivo*: a *Caenorhabditis elegans* study. Environ Sci Nano:1

Falkinham JO, Wall TE, Tanner JR, Tawaha K, Alali FQ, Li C (2009) Proliferation of antibiotic producing bacteria and concomitant antibiotic production as the basis for the antibiotic activity of Jordan's red clays. Appl Environ Microbiol 75:2735–2741

Farris PK (2016) Are skincare products with probiotics worth the hype? Dermatology Times, viitattu. http://dermatologytimes.modermedicine.com/dermatology-times/news/skincare-products-probiotics

Feleke BE (2017) Determinants of Podoconiosis: a case control study. Ethiop J Health Sci 27(5):501–506

Feng QL, Wu J, Chen GQ, Cui FZ, Kim TN, Kim JO (2000) A mechanistic study of the antibacterial effect of silver ions on *Escherichia coli* and *Staphylococcus aureus*. J Biomed Res 52(4):662–668

Fernández-Gonzalez MV, Martin-Garcia JM, Delgado G, Párraga J, Delgado R (2007) A study of the chemical, mineralogical and physicochemical properties of peloids prepared with two medicinal mineral waters from Lanjarón Spa (Granada, Spain). Appl Clay Sci 80-81:107–116

Fernández-Gonzalez MV, Martin-Garcia JM, Delgado G, Párraga J, Carretero MI, Delgado R (2013) Una aproximación al estabelecimento de los tempos óptimos de maturación. Livro de Actas do III Congresso Iberoamericano de Peloides. Nunes J, Gomes C. Silva J. (eds), Ponta Delgada, São Miguel, Açores, 127–131

Fernández-Lao C, Cantarero I, Garcia JF, Arroyo M (2012) Termoterapia. In: Albornoz M, Meroño J: Procedimientos generales de fisioterapia. Elsevier, Barcelona, pp 53–65

Fernandez-Torán MA (2014) Propiedades físico-quimicas de materiales susceptibles de ser utilizados en la preparación de peloides. PhD thesis, Universidad Complutense de Madrid, 250 pp

Ferrand T, Yvon J (2000) Thermal properties of clay pastes for pelotherapy. Appl Clay Sci 6:21–38

Ferreira L, Fonseca AM, Botelho G, Almeida-Aguiar C, Neves IC (2012) Antimicrobial activity of faujasite zeolites doped with silver. Microporous Mesoporous Mater 160:126–132. https://doi.org/10.1016/j.micromeso.2012.05.006

Ferrell RE (2008) Medicinal clay and spiritual healing. Clay Clay Miner 56:751–760

Figueiredo BR, Litter MI, Silva CR, Mañay N, Londono SC et al (2010) Medical geology studies in South America. In: Selinus O, Finkelman RB, Centeno JA (eds) Medical geology: regional synthesis. Springer, Dordrecht/Heidelberg/London/New York, pp 79–106. https://doi.org/10.1007/978-90-481-3430-4. ISBN 978-90-481-3429-8 e-ISBN 978-90-481-3430-4

Finkelman RB (2019) The influence of clays on human health: a medical geology perspective. Clays and clay minerals 58 (2), J Clay Minerals Soc, ISSN 0009-8604. https://doi.org/10.1007/s42860-018-0001-9

Fioravanti A, Chelesschi S (2015) Mechanisms of action of balneotherapy in rheumatic diseases. Balnea 10:43–56

Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M (2011) Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int 31(1):1–8

Fioravanti A, Giannitti C, Bellisai B, Iacoponi F, Galeazzi M (2012) Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. Int J Biometeorol 56(4):583–590

Fioravanti A, Lamboglia A, Pascarelli NA (2013) Thermal water of Vetriolo, Trentino, inhibits the negative effect of interleukin 1β on nitric oxide production and apoptosis in human osteoarthritic chondrocytes. J Biol Regul Homeost Agents 27:891–902

Fioravanti A, Tenti S, Gianitti C, Fortunati NA, Galeazzi M (2014) Short and long-term effects of mud-bath treatment on hand osteoarthritis: a randomized clinical trial. Int J Biometeorol 58(1):79–86

Flerer N, Jackson RB (2006) The diversity and biogeography of soil bacterial communities. Proc Natl Acad Sci U S A 103:626–631. https://doi.org/10.1073/pnas.0507535103

Flusser D, Abu-Shakra M, Friger M, Codish S, Sukenik S (2002) Therapy with mud compresses for knee osteoarthritis: comparison of natural mud preparations with mineral-depleted mud. J Clin Rheumatol 8(4):197–203

Forestier R, Françon A (2008) Crenobalneotherapy for limb osteoarthritis: systematic literature review and methodological analysis. Joint Bone Spine 75:138–148

Forestier R, Forestier FB, Francon A (2016) Spa therapy and knee osteoarthritis: a systematic review. Ann Phys Rehab 59(3):216–226

Fraioli A, Mennuni G, Fontana M, Nocchi S, Ceccarelli F, Perricone C, Serio A (2018) Efficacy of spa therapy, mud-pack therapy, balneotherapy, and mud-bath therapy in the management of knee osteoarthritis. A systematic review. Biomed Res Int:1042576

François G, Micollier A, Rouvie I (2005). Les Boues Thermales, Atelier Santé Environmental, ENSP (École Nationale de la Santé Publique), Rennes, 29pp

Friedlander LR, Puri N, Martin A, Schoonen A, Karzai AW (2015) The effect of pyrite on Escherichia coli in water: proof-of-concept for the elimination of waterborne bacteria by reactive minerals. J Water Health 13(1). https://doi.org/10.2166/wh.2014.013

Galán E (1996) Properties and applications of palygorskite-sepiolite clays. Clay Miner 31:443–453

Gálvez I, Torres-Piles S, Ortega E (2019) Effect of mud-bath therapy on the innate/inflammatory responses in elderly patients with osteoarthritis: a discussion of recent results and a pilot study on the role of the innate function of monocytes. Int J Biometeorol. https://doi.org/10.1007/s00484-019-01748-4

Galzigna L, Moretto C, Lalli A (1996) Physical and biochemical changes of thermal mud after maturation. Biomed Pharmacother 50(6–7):306–308

Galzigna L, Bettero A, Bellometti S (1999a) La maturation de la boue thermale et sa mesure. Première partie. Press Therm Clim 136(1):23–26

Galzigna L, Bettero A, Bellometti S (1999b) La maturation de la boue thermale et sa mesure. Deuxième partie. Press Therm Clim 136(1):27–30

Ganju P, Nagpal S, Mohammed MH, Kumar PN, Pandey R, Natarajan VT (2016) Microbial community profiling shows dysbiosis in the lesional skin of vitiligo subjects. Sci Rep 6

Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ (2008) Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS One 3:e2719

Garcia PT (2014) Peloterapia en Cosmética y Medicina Estética. In: Peloteraia: Aplicaciones médicas y cosméticas de fangos termales. Fundación Bílbilis, Torres, A.H. (coordinador), pp 185–207

Garcia-Villén F, Faccendini A, Miele D, Ruggeri M, Sánchez-Espejo R, Borrego-Sánchez A, Cerezo P, Rossi S, Viseras C, Sandri G (2020) Wound healing activity of nanoclay/spring water hydrogels. Pharmaceuticals, MDPI 12:467. https://doi.org/10.3390/pharmaceuticals12050467

Garcia Rodriguez ML, Álvarez Garcia B (2019) Origen y distribución de arcillas utilizadas en la fabricación de búcaros: bucarophagy in early modern times. Physis Terrae 1(1):57–71. ISSN: 2184-626X, http://revistas.uminho.pt/index.php/physisterrae/index

Garcidueñas-Pina R, Cervantes C (1995) Microbial interactions with aluminum. Biometals 9:311–316

Gaskel EE, Hamilton AR, Hutcheon GA, Roberts M (2012) Antibacterial properties of cu- and Zn-exchanged laponites® 6th mid-European clay conference (MECC'12), Průhonice near Prague, September 2012, Czech Republic, M. Šťastný a A. Žigová (eds.) 87

Gautier T (1845) Voyage en Espagne, 1840−1845 Charpentier, Paris, 1845

Geissler PW, Mwaniki DL, Thiong'o F, Michaelsen KF, Friis H (1997) Geophagy, iron status and anemia among primary school children in western Kenya. Tropical Med Int Health 3(7):529–534

Geissler P, Shulman C, Prince R, Mutemi W, Mnazi C, Friis H, Lowe B (1998) Geophagy, iron status and anaemia among pregnant women on the coast of Kenya. Trans R Soc Trop Med Hyg 92:549–553

Geissler PW, Prince RJ, Levene M, Poda C, Beckerly SE, Mutemi W, Schulman CE (1999) Perception of soil eating and anaemia among pregnant women on the Kenyan coast. Soc Sci Med 48(8):1069–1079

George KM, Barker LP, Welty DM, Small PLC (1998) Partial purification and characterization of biological effects of a lipid toxin produced by *Mycobacterium ulcerans*. Infect Immun 66(2):587–593

George KM, Chatterjee D, Gunawardana G, Welty D, Hayman J, Lee R, Small PLC (2002) Mycolactone: a polyketide toxin from Mycobacterium ulcerans, required for virulence. Science 283(5403):854

Gerencser G, Muranyiu E, Szendi K, Varga C (2010) Ecotoxicological studies on Hungarian peloids (medicinal muds). Appl Clay Sci 50(1):47–50

Ghadiri M, Chrzanowski W, Rohawizadeh R (2015) RSC Advances, issue:37

Ghorbani H (2008) Geophagia, a soil – environmental related disease . International Meeting on Soil Fertility Land Management and Agroclimatology. Turkey, 957–967

Giotakos O et al (2015) Lithium in the public water supply and suicide mortality in Greece. Biol Trace Elem Res 156(1–3):376–379

Glavas N, Mourelle ML, Gómez CP, Legido JL, Smuc NR, Dolenec M, Kovac N (2017) The mineralogical, geochemical, and thermophysical characterization of healing saline mud for use in pelotherapy. Appl Clay Sci 135:119–128

Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H, Carr AJ (2015) Osteoarthritis. Lancet 386(9991):376–387

Gomes CSF (2002) Argilas: Aplicações na Indústria. O Liberal (editor), Câmara de Lobos, R.A. da Madeira, 377 pp

Gomes CSF (2015) In pelotherapy what is more important, the peloid solid phase or the peloid liquid phase? Balnea 10:125–142

Gomes CSF (2018) Healing and edible clays: a review of basic concepts, benefits and risks. Journal Environmental Geochemistry and Health, Springer

Gomes de Melo BA, Lopes Motta F, Andrade Santana MH (2015) Humic acids: structural properties and multiple functionalities for novel technological developments. Mater Sci Eng C62:967–974

Gomes CSF, Silva JBP (2007) Minerals and clay minerals in medical geology. Appl Clay Sci, Elsevier 36:4–21

Gomes CSF, Hernandez R, Sequeira MC (2009) Characterization of clays used for medicinal purposes in the Archipelago of Cape Verde. Geochim Bras 22(3):315–331

Gomes CSF, Silva JBP, Gomes JHC (2015) Natural peloids versus designed and engineered peloids. Bol Soc Esp Hidrol Méd 30(1):15–36

Gomes CSF, Gomes JH, Silva EF (2019) Bactericidal Peloid and Ointment based on Kaolin and Thermal Mineral Water to be Used in the Treatment of Infectious Skin Wounds**.** Abstract Book of the International Symposium on Thermalism and Quality of Life (STCV-2019), Universidad de Vigo, Campus de Ourense

Gomes CSF, Gomes JH, Silva EF (2020) bacteriostatic and bactericidal clays: An overview. Environ Geochem health, published online 30 June 2020, 21pp. Springer Nature BV. https://doi.org/10.1007/s10653-020-00628-w

Gómez CP, Maraver F, Vela L, Carretero I, Nunes JC, Silva JB, Gomes C, Mourelle ML, Legido JL (2019) 10 años de Congreso Iberoamericano de Peloides. Bol Soc Esp Hidrol Med 34(2):129–136. https://doi.org/10.23853/bsehm.2019.0959

Governa M, Valentino M, Visonà I, Monaco F, Amati M, Scancarello G, Scansetti G (1995) In vitro biological effects of clay minerals advised as substitutes for asbestos. Cell Biol Toxicol 11:237–249

Greenblatt MD (2018) Integrative Medicine for Alzheimer's: the breakthrough natural treatment plan that prevents Alzheimer using nutritional Lithium" 176pp

Grewal S, Bhagat M, Vakhlu J (2014) Antimicrobial protein produced by *Pseudomonas aeruginosa* JU-Ch 1, with a broad spectrum of antimicrobial activity. Biocatal Agric Biotech 3:332–337

Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC (2009) Topographical and temporal diversity of the human skin microbiome. Science 324:1190–1192

Grigsby RK, Thyer BA, Waller RJ, Johnston GA Jr (1999) Chalk eating in middle Georgia: a culture-bound syndrome of pica? South Med J 92:190–192

Guimarães F, Guimarães L (1954) Hidrologia Médica. Edição do Instituto de Climatologia e Hidrologia da Universidade de Coimbra, Coimbra

Gundacker C, Kutalek R, Glaunach R, Deweis C, Hengstschlager M, Prinz A (2017) Geophagy during pregnancy: is there a health risk for infants? Environ Res 156:145. https://doi.org/10.1016/j.envres2017.03.028

Guthrie GD (1992) Biological effects of inhaled minerals. Am Mineral 77:225–243

Halsted JA (1968) Geophagia in man: its nature and nutritional effects. Am J Clin Nutr 21:1384–1393

Hanif M, Jabbas F, Sharif S, Abbas G, Farooq A, Aziz M (2016) Halloysite nanotubes as a new drug-delivery system: a review. Clay Miner 51(3):469–478

Hári J, Polyák P, Mester D, Micusik M, Omastová M, Kállay M, Pukánsky B (2016) Adsorption of an active molecule on the surface of halloysite for controlled release application: interaction, orientation, consequences. Appl Clay Sci 132-133:167–174

Harini K, Ajila V, Hedge S (2013) Bdellovibrio bacteriovorus: A future antimicrobial agent? J Indian Soc Periodontal 17(6):823–825

Hassen A, Saidi N, Cherifh M, Boudabous A (1998) Effects of heavy metals on Pseudomonas aeruginosa and Bacillus thuringiensis. Bioresour. Technol, vol 65. Elsevier Science, pp 73–82

Hauser EA (1950) Canamin clay and its properties. Can Chem Process Ind 34:979

Hauser EA (1952) Kisameet Bay clay deposit. Problems of Clay and Laterite genesis, Symposium at Annual Meeting of the American Institute of Mining and Metallurgical Engineers, St Louis, MO, In, pp 178–190

Haydel SE, Remenih CM, Williams LB (2008) Broad-spectrum *in vitro* antibacterial activities of clay minerals against antibiotic-susceptible and antibiotic-resistant bacterial pathogens. J Antimicrob Chemother 61:353–361

Health Canada (2012) Guidance on heavy metal impurities in cosmetics. http://www.hc-sc.gc.ca/cps-spc/pubs/indust/heavy_metalsmetaux_lourds/index-eng.php

Henry JM, Cring D (2013) Chapter 8: Geophagy: an anthropological perspective. In: Brevik EC, Burgess LC (eds) Soils and human health. CRC Press, Taylor & Francis Group

Hernández D, Lazo L, Valdés L, Ménorval LC, Rozynek Z, Rivera A (2018) Synthetic clay mineral as nanocarrier of sulfamethoxazole and trimethoprim. Appl Clay Sci 161:395–403

Holešová S, Hundáková M, Pazdziora E (2016) Antibacterial kaolinite-based nanocomposites. Procedia materials science, vol 12. Elsevier, pp 124–129

Hollinger MA (1990) Pulmonary toxicity of inhaled and intravenous talc. Toxicol Lett 52:121–127

Hooda PS, Henry CJK, Seyoum TA, Armstrong LDM, Fowler MB (2002) The potential impact of geophagia on the bioavailability of iron, zinc and calcium in human nutrition. Environ Geochem Health 24:305–319

Hooda PS, Henry CJK, Seyoum TA, Armstrong LDM, Fowler MB (2004) The potential impact of soil ingestion on human mineral nutrition. Sci Total Environ 333:75–87

Horno MAP (2014) Historia de la Peloterapia. In: Peloterapia: Aplicaciones médicas y cosméticas de fangos termales. Torres AH (coordinador), Fundación Bílbilis, pp 47–53

Hrenovic J, Milenkovic J, Goic-Barisic I, Rajic N (2013) Antibacterial activity of containing natural zeolite against clinical isolates of Acinetobacter baumannii. Microporous Mesoporous Mater 169:148–152

Hu CH, Xia MS (2006) Adsorption and antibacterial effect of copper-exchanged montmorillonite on Escherichia coli K-88. Appl Clay Sci 31:180–184

Hu CH, Xu ZR, Xia MS (2005) Antibacterial effect of Cu2+−exchanged montmorillonite on *Aeromonas hydrophila* and discussion on its mechanism. Vet Microbiol 109:83–88

Huebl L, Leick S, Guettl L, Akello G, Kutalek R (2016) Geophagy in northern Uganda: perspectives from consumers and clinicians. Am J Trop Med Hyg 95(6):1440–1449

Humboldt A (1985) [1799] Viaje a las Regiones Equinocciales del Nuevo Continente. Caracas: Monte Ávila Editores, T. 4, 601 p. (translated by Lisandro Alvarado)

Hunter JM (1973) Geophagy in Africa and United States: a culture-nutrition hypothesis. Geogr Rev 63:170–195

Hunter JM, De Kleime R (1984) Geophagy in Central America. Geogr Rev 74:157–169

Igeoma KH, Onyoche OE, Uju OV, Chukwuene IF (2014) Assessment of heavy metals in edible clays sold in Onitsha metropolis of Anambra state, Nigeria. Br J Appl Sci Technol 4(14):2114–2124

Izugbara CO (2003) The cultural context of geophagy among pregnant and lactating Ngwa women of southeastern Nigeria. Afr Anthropol 10(2):180–199

Jayrajsinh S, Pharm G, Agrawal Y, Bakre L (2017) Montmorillonite nanoclay as a multifaceted drug-delivery carrier: a review. J Drug Deliv Sci Technol 39:200–209

Jeong JH, Lee CY, Chung DK (2016) Probiotic lactic acid bacteria and skin health. Crit Rev Food Sci Nutr 56:2331–2337

Johns T (1986) Detoxification functions of geophagy and domestication of the potato. J Chem Ecol 12:635–646

Johns T, Duquette M (1991) Detoxification and mineral supplementation as functions of geophagy. Am J Clin Nutr 53:448–456

Jokić A, Sremcević N, Karagülle Z, Pekmezović T, Davidović V (2010) Oxidative stress, hemoglobin content, superoxide dismutase and catalase activity influenced by Sulphur baths and mud packs in patients with osteoarthritis. Vojnosanit Pregl 67:573–578

Jones TP, Berube KA, Wlodarczyk AJ, Prytherch ZC, Hassan Y, Potter S, Adams R (2015) The bioreactivity of “red clays” from basaltic terrains. EuroClay conference 2015, proceedings. In: Williams L, Jones T, Rocha F (eds) Bioreactive clay mineral impacts on environmental and human health. Edinburgh, Scotland, p 137

Jumbam ND (2013) Geophagic materials: the possible effects of their chemical composition on human health. Trans R Soc South Africa 68:177–182

Jung WK, Koo HC, Kim KW, Shin S, Kim SH, Park YH (2008) Antibacterial activity and mechanism of action of the silver ion in *Staphylococcus aureus* and *Escherichia coli*. Appl Environ Microbiol 74:2171–2178. https://doi.org/10.1128/AEM.02001.07

Jurinski JB, Rimstidt JD (2001) Biodurability of talc. Am Mineral 86:392–399

Kabacs N, Memon A, Obinwa T et al (2011) Lithium in drinking water and suicide rates across the East of England. Br J Psychiatry 198:406–407

Kalinowski BE, Bengtsson A, Pedersen K, Lilja C, Sellin P, Sjoland A (2016) Threshold density for microbial sulphate reduction in bentonite. In: Goldschmidt Conference Proceedings, Yokohama, Abstract n° 771

Kambunga SN, Candeias C, Hasheela I, Mouri H (2019) Review of the nature of some geophagic materials and their potential health effects on pregnant women: some examples from Africa. Environ Geochem Health. https://doi.org/10.1007/s10653-019-00288-5

Kamitsou MD, Sygouni V, Kanellopoulou DG, Gardikis K, Koutsoukos KPG (2018) Physicochemical characterization of sterilized muds for pharmaceutics/cosmetics applications. Environ Geochem Health 40:1449–1464

Kapusta ND et al (2011) Lithium in drinking water and suicide mortality. Br J Psychol 198(5):346–350

Karakaya MC, Doğru M, Karakaya N, Vural HC, Kuluöztürk F, Bal SS (2015) Radioactivity concentrations and dose assessments of therapeutic peloids from some Turkish spas. Clay Miner 50:221–232

Karpińska M, Kapala MJ, Raciborska A, Kulesza G, Milewska A, Mnich S (2017) Radioactivity of natural medicinal preparations contained extracts from peat mud available in retail trade used externally. Nat Prod Res 31:1935–1939

Key TC Jr, Horger EO III, Miller JM (1982) Geophagia as a cause of maternal death. Obstet Gynaecol 60:525–526

Khurama C, Vela A, Andhariye N, Pandey OPCB (2014) Antibacterial activity of silver: the role of hydrodynamic particle size at nanoscale. J Biomed Mater Res A 102:3361–3368

Kikouama OJR, Baldé L (2010) From edible clay to clay-containing formulation for optimization of the Oral delivery of some trace elements: a review. Int J Food Sci Nutr 61(8):1–21

Kikouama OJR, Le Cornec F, Bouttier S, Launay A, Baldé L, Yagoubi N (2009) Evaluation of trace elements released by edible clays in physicochemically simulated physiological media. Int J Food Sci Nutr 60(2):130–142

Kikouama OJR, Le Cornec F, Bouttier S, Launay A, Baldé L, Yagoubi N (2009a) Evaluation of trace elements released by edible clays in physicochemically simulated physiological media. Int J Food Sci Nutr 60(2):130–142

Kikouama OJR, Konan KL, Katty A, Bonnet JP, Baldé L, Yagoubi N (2009b) Physicochemical characterization of edible clays and release of trace elements. Appl Clay Sci 43(1):135–141

Kim JH, Lee J, Lee HB, Shin JH, Kim EK (2010) Water-retentive and anti-inflammatory properties of organic and inorganic substances from Korean sea mud. Nat Prod Commun 5(3):395–398

Korevaar DA, Visser BJ (2012) Podoconiosis, a neglected disease. Neth J Med 70(5):210–214

Kostyniak P, Constanzo PM, Syracuse J, Giese R (2003) Antimicrobial activity of modified clay minerals. Abstract in Clays and Clay minerals Annual Meeting, Athens Ga

Kutalek R, Wewalka G, Gundacker C, Auer H, Wilson J, Haliza D, Huhulescu S, Hillier S, Sager M (2010) Geophagy and potential health implications: geohelminths, microbes and heavy metals. Trans R Soc Trop Med Hyg 104(12):787–795

Kwakye-Awuah B, Williams C, Kenward MA, Radecka I (2008) Antimicrobial action and efficiency of silver-loaded zeolite X. J Appl Microbiol 104:1516–1524

Kwong AM, Henry J (2003) Why is geophagy treated like dirt? Deviant Behav 24:353–371. https://doi.org/10.1080/713840222.l

Lafi SA, Al-Dulaimy MR (2011) Antibacterial effect of some mineral clays in vitro. Egypt Acad J Biol Sci 3(19):75–81

Lambert V, Boukhari R, Misslin-Tritsch C, Carles G (2013) La géophagie: advances dans la comprehension de ses causes et consequences. La Revue de Médicine Interne 34:94–98

Lansdown ABG (2006) Silver in health care: antimicrobial effects and safety in use. Curr Probl Dermatol 33:17–34

Lar UA, Agene JI, Umar AI (2014) Geophagic clay materials from Nigeria: a potential source of heavy metals and human health implications in mostly women and children who practice it. Environ Geochem Health 37:363–375. https://doi.org/10.1007/s10653-014-9653-0

Laufer B (1930) Geophagy. Field Museum of natural history, publication 280. PhD Thesis Anthropology Series 18, 99–198

Legido JL, Mourelle ML (eds.) (2008) Investigaciones en el ámbito Iberoamericano sobre Peloides termales. Universidad de Vigo, 308 pp

Legido JL, Medina C, Mourelle L, Carretero MI, Pozo M (2007) Comparative study of the cooling rates of bentonite, sepiolite and common clays for their use in pelotherapy. Appl Clay Sci 36:148–160

Lemire JA, Harrison JJ, Turner RJ (2013) Antimicrobial activity of metals: mechanisms, molecular targets and applications. Nat Rev Microbiol 11:371–384

Letaief S, Detellier C (2013) Kaolinite-polymer nanocomposites. In: Bergaya F, Lagaly G (eds) Developments of clay science v.5A, Handbook of clay science, 2nd edn. Elsevier, Oxford, pp 707–719

Lewis J (1935) Thermal properties of peloids. Arch Med Hydrol 8:181

Li SJ, Yang LS, Li YH, Wang WY, Xirao RD (2006) Relationship between the content of selenium in grains and the Kashin–Beck disease in Tibet, China. Chin J Endemiol 25(6):673–674

Li SJ, Li W, Hu X, Yang L, Xirao R (2009) Soil selenium concentration and Kashin-Beck disease prevalence in Tibet, China. Front Environ Sci Eng China 3:62–68

Lim DG, Jeong WW, Kim NA, Lim JY, Lee SH, Shim WS, Kang NG, Jeong SH (2014) Effect of the glyceryl monooleate-based lyotropic phases on skin permeation using in vitro diffusion and skin imaging. Asian J Pharm Sci 9:324–329

Liu H, Zeng C, Gao SG, Yang T, Luo W, Li YS (2013) The effect of mud therapy on pain relief in patients with knee osteoarthritis: a meta-analysis of randomized controlled trials. J Int Med Res 41:1418–1425

Londoño SC (2007) Caracterización Geoquímica Preliminar De Las Arcillas Con Potencial De Uso Medicinal Presentes En Araracuara, Caquetá, Colombia. BSc Monograph, Geology Program, Universidad Nacional, Bogotá, Colombia

Londono SC, Williams L (2015) Evaluating the antibacterial action of a clay from the Colombian Amazon, International Applied Geochemistry Symposium, April 2015, 7pp

Londono SC, Williams LB (2016) Unraveling the antibacterial mode of action of a clay from Colombian Amazon. Environ Geochem Health 38:363–379

Londono SC, Hartnett HH, Williams LB (2017) The antibacterial activity of aluminium in clay from Colombian Amazon. Environ Sci Technol 51:2401–2408. https://doi.org/10.1021/acs.est.6b04670

Lopez-Galindo A, Viseras C (2004) Pharmaceutical and cosmetic application of clays. In: Wypych F, Satyanarayana KG (eds) Clay surfaces: fundamentals and applications. Elsevier, Amsterdam, pp 267–289

Lopez-Galindo A, Viseras C, Cerezo P (2007) Compositional, technical and safety specifications of clays to be used as pharmaceutical and cosmetic products. Appl Clay Sci 36:51–63

Lucera A, Costa C, Conte A, Del Nobile MA (2012) Food applications of natural antimicrobial compounds. Front Microbiol vol 3, article 287(1)

Lv Y, Tao Y, Yang Z, Zhao W, Zhang M, Wang Q (2014) Constraint on selenium bioavailability caused by its geochemical behavior in typical Kashin-Beck disease areas in Aba, Sichuan Province of China. Sci Total Environ 493:737–749

Lv XL, Zhang J, Gao WY, Xing WM, Yang ZX, Yue YX, Wang YZ, Wang GT (2018) Association between osteoporosis, bone mineral density levels and Alzheimer's disease: a systematic review and meta-analysis. Int J Gerontol 12:76–83

Lvov Y, Price R (2015) Halloysite nanotubes: Applications in nanomaterial research. Institute for Micromanufacturing, Louisiana, Tech. Univ., USA

Lvov Y, Wang W, Zhang L, Fakhrullin R (2016) Halloysite nanotubes for loading and sustained release of functional compounds. Adv Mater 28(6):1227–1250

Lyles MP (2018) Biological, chemical and environmental hazards of desert dust to military personnel. In: De Vivo B, Belkin HE, Lima A (eds) Environment geochemistry, 2nd edn. Elsevier, Amsterdam, pp 467–485

Ma'or Z, Henis Y, Along Y, Orlov E, Sorensen KB, Oren A (2006) Antimicrobial properties of Dead Sea black mineral mud. Int J Dermatol 45:504–511

Ma'or Z, Halicz L, Portugal-Cohen M, Russo MZ, Robino F, Vanhaecke T, Rogiers V (2015) Safety evaluation of traces of nickel and chrome in cosmetics: the case of Dead Sea mud. Regul Toxicol Pharmacol 73:797–801

Macheka LR, Olowoyo JO, Matsela L, Khine AA (2016) Prevalence of geophagia and its contributing factors among pregnant women at Dr. George Mukhari Academic Hospital, Pretoria. Afr Health Sci 16:972–978

Magana SM, Quintana (2008) Antibacterial activity of montmorillonites modified with silver. J Mol Catal A Chem 281:192–199

Magalotti L (1825) Varie operetta del Conte Lorenzo Magalotti con giunta di otto lettere sulle terra odorosa d'Europa e d'America volgarmente dette biccheri e ora pubblicate per la prima volta. Giovanni Silvestrini, Milano, 1825, Lettera ottava, pp 455

Mahaney WC, Milner MW, Mulyono HS, Hancock RGV, Aufreiter S, Reich M, Wink M (2000) Mineral and chemical analyses of soils eaten by humans in Indonesia. Int J Environ Health Res 10:93–109

Mahboob N, Sousan K, Shirzad A, Amir G, Mohammad V, Reza M, Mansour VA, Hadi V (2009) The efficacy of a topical gel prepared using Lake Urmia mud in patients with knee osteoarthritis. J Altern Complement Med 15:12391242

Malachová K, Praus P, Rybková Z, Kosák O (2011) Antibacterial and antifungal activities of silver, copper and zinc montmorillonite. Appl Clay Sci 53:642–645

Manderson L, Aaraard-Hansen J, Allotey P (2009) Social research on neglected diseases of poverty: continuing and emerging themes. PLoS Neglect Trop Dis:e332

Maraver F (2006) Antecedentes históricos de la Peloterapia. Anales de Hidrlogia Médica 1:17–42

Maraver F (2008) El agua mineromedicinal: Una herramienta curativa milenaria. Tribunatermal 11:54–57

Maraver F (2013) Mechanisms of action of pelotherapy: state of the art. In: Nunes J, Gomes C, Silva J (eds) Livro de Actas do III Congresso Iberoamericano de Peloides. Ponta Delgada, São Miguel, Açores, pp 9–18

Maraver F (2017) Investigación actual en peloterapia. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, España, 33–35

Maraver F, Fernandez-Torán MA, Corvillo I, Morer C, Váquez I, Aguillera L, Armijo F (2015) Peloterapia: Una Revisión. Med Nat 9(1):38–46

Mascolo N, Summa V, Tateo F (1999) Characterization of toxic elements in clays for human healing use. Appl Clay Sci 15:491–500

Mascolo N, Summa V, Tateo F (2004) In vivo experimental data on the mobility of hazardous chemical elements from clays. Appl Clay Sci 25:23–28

Massaro M, Lazzara G, Milioto S, Noto R, Riela S (2017) Covalently modified halloysite clay nanotubes: synthesis, properties, biological and medical applications. J Mater Chem B5:2867–2882. https://doi.org/10.1039/C7TB90071F

Massaro M, Campofelice A, Colletti CG, Lazzara G, Noto R, Riela S (2018a) Functionalized halloysite nanotubes: efficient carrier systems for antifungine drugs. Appl Clay Sci 160:186–192

Massaro M, Colletti CG, Lazzara G, Riela S (2018b) The use of some clay minerals as natural resources for drug carrier applications. J Func Biomater 9:58. https://doi.org/10.3390/jfb9040058

Masurat P, Ericksson S, Pedersen K (2010) Microbial sulphide production in compacted Wyoming bentonite MX-80 under in situ conditions relevant to a repository for high-level radioactive waste. Appl Clay Sci 47:58–64

Matas AG, Torres AH, Úbeda JCB (2014) Peloterapia: Conceptos generales, terminología, clasificación. In: Peloterapia: Aplicaciones médicas y cosméticas de fangos termales. Torres AH (coordinator). Ed, Fundación Bílbilis, Madrid, pp 19–31

Matz H, Orion E, Wolf R (2003) Balneotherapy in dermatology. Dermatol Ther 16(2):132–140

Maxim LD, Niebo R, McConnelll EE (2016) Bentonite toxicology and epidemiology: a review. J Inhal Toxicol 28(3):591–617

McInnes AD (2012) Diabetic foot disease in the United Kingdom: about time to put feet first. J Foot Ankle Res 5:26

Meijide R, Salgado T, Lianes A, Legido JL, Mourelle ML, Gómez C (2010) Evaluación de los câmbios en la piel trás la aplicación de peloides mediante métodos de bioengenharia cutânea. In: Maraver F, Carretero MI (eds) Libro de Resúmenes del II Congreso Iberoamericano de Peloides. C.E.R.S.-A, Madrid, pp 48–49

Meijide R, Mourelle ML, Vela-Anero A, López EM, Burguera EF, Pérez CG (2014) Aplicación a pacientes: Peloterapia en patologias dermatológicas. In: Peloterapia: Aplicaciones médicas y cosméticas de fangos termales. Fundación Bílbilis, Coordinator, Torres AH, pp 169–183

Meijide R, Burguera EF, Vela-Anero A (2015) Peloterapia y Artrosis. Balnea 10:289–300

Metge D, Harvey R, Eberl D, Williams L (2007) Bactericidal properties of clays used for treatment of Buruli ulcer-an emerging public health threat. Geological Society of America, Abstracts of Denver, Colorado, Meeting

Michaelis de Vasconcellos C (1905) Algumas palavras a respeito de púcaros de Portugal. Bulletin Hispanique, tome 7(2):140–196

Michele D, Giacomino M, Untura-Filho M, Beldarrain A (2006) Efectos sistémicos de los fangos minerales. Revisión de la literatura de los últimos 10 años/Systemics effects of minerals muds. A ten years literature review. Anales de Hidrología. Medica 1:135–142

Mihranyan A, Ferraz N, Strømme M (2012) Current status and future prospects of Balnea 10, nanotechnology in cosmetics. Prog Mater Sci 57(5):875–910

Milenkovic J, Hrenovic J, Matijasevic D, Niksic M, Rajic N (2017) Bactericidal activity of Cu-, Zn-, and Ag-containing zeolites toward Escherichia coli isolates. Environ Sci Pollut Res 24:20273–20281

Mishra BB, Roy R (2015) Soil science vs Science for medicine. EC Agri 2(5):454–461

Mishra BB, Kibret K, Feyissa S, Roy R (2017) Clinical relevance of type specific clays. Biomed J Sci Technol Res 1(5). https://doi.org/10.26717/BISTR.2017.01.000455

Moghadas B, Dashtimoghhadam E, Mirzadeh H, Farzad S, Mohammad M et al (2016) Novel chitosan-based nanobiohybrid membranes for wound dressing applications. RSC Adv 6:7701–7711

Molla YB, Wardrop NA, Le Blond JS, Baxter P, Newport MJ, Atkinson PM, Davey G (2014) Modelling environmental factors correlated with podoconiosis: a geospatial study of non-filarial elephantiasis. Int J Health Geogr 13:24

Morer C, Roques C-F, Françon A, Forestier R, Maraver F (2017) The role of mineral elements and other chemical compounds used in balneology: data from double-blind randomized clinical trials. Int J Biometeorol, Springer, ISSN 0020-7128, https://doi.org/10.1007/s00484-017-1421-2.D

Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramirez JT, Yacaman MJ (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16:2346–2353

Morrison KD, Underwood JC, Metge DW, Eberl DD, Williams LB (2013) Mineralogical variables that control the antibacterial effectiveness of a natural clay deposit. Environ. Geochem. Health. https://doi.org/10.1007/s10653-013-9585-0, Springer

Morrison KD, Misra R, Williams LB (2016) Unearthing the antibacterial mechanism of medicinal clay: a geochemical approach to combating antibiotic resistance. Sci Rep 6:19043. https://doi.org/10.1038/Srep19043

Morrison KD, Williams SN, Williams LB (2017) The anatomy of an antibacterial clay deposit: a new economic geology. Econ Geol 112(7):1551–1570

Munñoz SM, Melián C, Gelen A, Diaz O, Martinez-Santos M, Ruiz-Romera E, Fagundo JR, Pérez-Gramatges A, Martinez-Villegas NV, Blanco D, Hernández R, González-Hernandez P (2015) Physicochemical characterization, element speciation and hydrogeochemical modeling of river and peloid sediments used for therapeutic uses. App Clay Sci 104:36–47. https://doi.org/10.1016/j.clay.2014.11.029

Musumeci G, Aiello FC, SzychlinskaMA DRM, Castrogiovanni P, Mobasheri A (2015) Osteoarthritis in the XXIst century: risk factors and behaviours that influence disease onset and progression. Int J Mol Sci 16(3):6093–6112

Mwalongo D, Mohamed NK (2013) Determination of essential and toxic elements in clay soil commonly consumed by pregnant women in Tanzania. Radiat Phys Chem 91:15–18

Naik A, Pechtold L, Potts R, Guy R (1995) Mechanism of oleic acid-induced skin penetration enhancement in vivo in humans. J Control Release 37:299–306

Nchito M, Geissler PW, Mubila L, Friis H, Olsen A (2004) Effects of iron and multimicronutrient supplementation on geophagy: a two-by-two factorial study among Zambian school-children in Lusaka. Trans R Soc Trop Med Hyg 98:218–227

Ngole VM, Ekosse GE, Jager L, Songca SP (2010) Physicochemical characteristics of geophagic clayey soils from South Africa and Swaziland. Afr. J Biotechnol 9(36):5929–5930

Nissenbaum A, Rullköetter J, Yechieli Y (2002) Are the curative properties of 'black mud' from the Dead Sea due to the presence of bitumen (asphalt) or other types of organic matter? Environ Geochem Health 24(4):327–335

Njiru H, Elchalal U, Paltiel O (2011) Geophagy during pregnancy in Africa: a literature review. Obstet Gynecol Surv 66:452–459

Nkansah MA, Korankye M, Darko G, Dodd M (2016) Heavy metal content and potential health risk of geophagic white clay from Kumasi Metropolis in Ghana. Toxicol Rep 3:644–651. https://doi.org/10.1016/j.toxrep.2016.08.005

Nnorom IC (2016) Major and minor element contents of Calabash clay (nzu) from Abia State, Nigeria: evaluation of potential intake benefits and risks. Toxicol Environ Chem 98:149–166. https://doi.org/10.1080/02772248.2005.1110157

Nordberg M, Cherian MG (2005) Biological responses of elements. In: Selinus O, Alloway B, Centeno JA, Finkelman RB, Fuge R, Lindh U, Smedley P (eds) Essentials of medical geology: impacts of the natural environment on public health, pp 179–200

Novelli, G (1996) Applicazion medicali e Igieniche delle bentoniti. Atti Conv. "Argille Curative", Veniale F. (editor), Gruppo Italiano AIPEA, Salice Terme (PV), Tipografia Trabella, Milano

Novelli G (1998) Applicazioni Cosmetiche e Medicaliu delle argille smectiche. Cosmetic News 122:350–357

Novelli G (2000) Bentonite: A clay over the centuries. Incontri Scentifici, V Corso di Formazione "Metodi di Analisi di Materiali Argillosi". Gruppo Itaiano AIPEA, 263–304

Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nusgart M, Cartwright D (2018) An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. Value Health 21:27–32

Nyanza EC, Joseph M, Premji SS, Thomas DS, Mannion C (2014) Geophagy practices and the content of chemical elements in the soil eaten by pregnant women in artisanal and small-scale gold mining communities in Tanzania. BMC Pregnancy Childbirth 14:144

O'Neill J (2016) Tackling drug-resistant infections globally: final report and recommendations of the review on antimicrobial resistance. Department of Health and the Wellcome Trust, UK

Odabasi E, Gul H, Macit E (2007) Lipophilic components of different therapeutic mud species. J Altern Complement Med (Mary Ann Liebert, Inc.) 13:1115–1118

Odabasi E, Turan M, Erdem H, Tekbas F (2008) Does mud pack treatment have any chemical effect? A randomized controlled clinical study. J Altern Complement Med 14(5):559–565

Odabasi E, Turan M, Erdem H, Pay S, Guleç M, Karagulle MZ (2009) The effect of mud pack treatment in knee osteoarthritis. Turk J Rheumatol 24:72–76

Odangowei OI, Okiemute O (2015) Geophagic practice and its possible health implications: a review. J Sci Multidiscip Res 7:100–110

Ökmen BM, Aksoy MK, Günes A, Eröksüz R, Altan L (2017) Effectiveness of peloid therapy in carpal tunnel syndrome: a randomized controlled single blind study. Int J Biometeorol 61:1403–1410

Oliveira KCBF, Meneguin AB, Bertolino LC, Filho ECS, Leite RSA, Eiras C (2018) Immobilization of biomolecules on natural clay minerals for medical applications. Int J Adv Med Biotechnol 1(1)

Onnainty R, Onida B, Páez P, Longhi M, Barresi A, Granero G (2016) Targeted chitosan-based bionanocomposites for controlled oral mucosal delivery of chlorhexidine. Int J Pharm 509:408–418

Otto CC, Haydel SE (2013a) Microbicidal clays: Composition, activity, mechanism of action, and therapeutic applications. In: Méndez-Vilas A (ed) Microbial pathogens and strategies for combating them: science, technology and education. FORMATEX, pp 1169–1180

Otto CC, Haydel SE (2013b) Exchangeable ions are responsible for the in vitro antibacterial properties of natural clay mixtures. PLOS ONE/wwwplosone 8(5):1–9

Otto CC, Koehl JL, Solanky D, Haydel SE (2014) Metal ions, non metal-catalyzed oxidative stress, cause clay leachate antibacterial activity. Plos One 9:e115172

Otto CC, Kilbourne J, Haydel SE (2016) Natural and ion-exchanged illite clays reduce bacterial burden and inflammation in cutaneous methicillin-resistant *Staphylococcus aureus* infections in mice. J Med Microbiol 65:19–27

Owumi SE, Oyelere AK (2015) Determination of metal ion contents of two antiemetic clays used in geophagy. Toxicol Rep 2:928–932

Özkuk K, Gürdal H, Karagülle M, Barut Y, Eröksüz R, Karagülle MZ (2017) Balneological outpatient treatment for patients with knee osteoarthritis; an effective non-drug therapy option in daily routine? Int J Biometeorol 61:719–728

Ozumba UC, Ozumba N (2002) Patterns of helminth infection in the human gut at the University of Nigeria Teaching Hospital, Enugu, Nigeria. J Health Sci 48:263–268

Padilla FV, Torre AM (2006) La pica: Retrato de una entidad clinica poco conocida. Nutr Hosp 21:547–692

Pandey A, Mittal A, Chauhan N, Alam S (2014) Role of surfactants as penetration enhancer in transdermal drug delivery. Mol Pharm Org Process Res 2:2

Panico V, Imperato R (2009) The psoriasis: a therapeutic alternative with sulphurous water of Terme Capasso. J Water Wellness 1(1):39–50

Panko AV, Kovzun IG, Ulberg ZR, Oleinik VA, Nikipelova EM, Babov KD (2016) Chapter 14: Colloid-chemical modification of peloids with nano-and microparticles of natural minerals and their practical use. In: Nanophysics, Nanophotonics, surface studies, and applications, Springer proceedings in Physics, vol 183, pp 163–177. https://doi.org/10.1007/978-3-319-30737-4-14

Pardo L, Domínguez-Maqueda M, Cecilia JA, Rodríguez MP, Osajima J, Miguel Moriñigo A, Franco F (2020) Adsorption of Salmonella in clay minerals and clay-based materials. Fortschr Mineral 10:130. https://doi.org/10.3390/min10020130

Parolo ME, Fernández LG, Zajonkovsky I, Sánchez MP, Baschini M (2011) Antibacterial activity of materials synthesized from clay minerals. In: Méndez-Vilas A (ed) Science against microbial pathogens: communicating current research and technological advances, pp 144–151

Pastor JM (1998) Termoterapia superficial. In: Martínez M, Pastor JM, Sendra F (eds) Manual de Medicina Fisica. Harcourt Brace, Madrid, pp 91–104

Pedersen K, Motamedi M, Karnland O, Sanden T (2000) Mixing and sulphate reducing activity of bacteria in swelling, compacted bentonite clay under high-level radiowaste repository conditions. J Appl Microbiol 89:1038–1047

Pena-Ferreira MR, Santos D, Silva JBP, Amaral MH, Sousa Lobo JM, Gomes JHCA, Gomes CSF (2010a) Aplicação de argilas esmectíticas da ilha do Porto Santo em máscaras faciais. In: Maraver F, Carretero MI (eds) Libro de resúmenes del II Congreso Iberoamericano de Peloides. C.E.R.S-A, Madrid, pp 30–31

Pena-Ferreira MR, Santos D, Silva JBP, Amaral MH, Sousa Lobo JM, Gomes JHCA, Gomes CSF (2010b) Desenvolvimento de formulações contendo argila esmectítica e areia carbonatada biogénica da ilha do Porto Santo para aplicação em máscaras de limpeza e branqueadoras. In: Maraver F, Carretero MI (eds) Libro de resúmenes del II Congreso Iberoamericano de Peloides. C.E.R.S-A, Madrid, pp 99–100

Pena-Ferreira MR, Santos D, Silva JBP, Amaral MH, Sousa-Lobo JM, Gomes JH, Gomes CSF (2011) Aplicações de argilas esmectíticas da ilha do Porto Santo em máscaras faciais. Anales de Hidrologia Médica 4:67–79

Pesciaroli C, Viseras C, Aguzzi C, Rodelas B, González-López J (2016) Study of the bacterial community structure and diversity during the maturation process of a therapeutic peloid. Appl Clay Sci 132:59–67

Photo-Jones E, Keane C, Jones AX, Stamatakis M, Robertson P, Hall AJ, Leanord A (2015) Testing Dioscorides' medicinal clays for their antibacterial properties: the case of Samian Earth. J Archaeol Sci 57:257–267

Pierchala MK, Makaremi M, Tan HL, Pushpamalar J, Muniyandy S, Solouk A, Lee SM, Pasbakhsh P (2018) Nanotubes in nanofillers: antibacterial multilayered polylactic acid/halloysite/gentamicin membranes for bone regeneration application. Appl Clay Sci 160:95–105

Porlezza C (1965) Considerazione sui fanghi terapeutici (peloidi). Thermae II 2–3:6–57

Pourabolghasem H, Ghorbanpour M, Shayegh R (2016) Antibacterial activity of copper-doped montmorillonite nanocomposites prepared by alkaline ion exchange method. J Phys Sci 27(2):1–12

Pozo M (2015) Importancia de la composición y propriedades físicas de las arcillas en la preparación de peloides. Balnea 10:187–206

Pozo M, Carretero MI, Pozo E, Marin Rubi JA, Maraver F (2010) Caracterización mineralógica y química de peloides españoles y argentinos: Evaluación de elementos traza potencialmente tóxicos. *En*: Libro de Resúmenes del II Congreso Iberoamericano de Peloides (Maraver, F. and Carretero, editores), Lanjarón, 2010, 37–38

Pozo M, Carretero MI, Maraver F, Pozo E, Gómez I, Armijo F (2013) Composition and physical-physicochemical properties of peloids used in Spanish spas: a comparative study. Appl Clay Sci 83-84:270–279

Prasad AS, Halsted JA, Nadimi M (1961) Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Am J Med 31:532–546

Price EW (1976) The association of endemic elephantiasis of the lower legs in East Africa with soil derived from volcanic rocks. Trans R Soc Trop Med Hyg:288–295

Price EW (1977) The site of lymphatic blockade in endemic (non-filarial) elephantiasis of the lower legs. J Trop Med Hyg 80:230–237

Price EW (1988) Non-Wlarial elephantiasis – confirmed as a geochemical disease, and re-named podoconiosis. Ethiop Med J 26:151–153

Price EW, Bailey D (1984) Environmental factors in the etiology of endemic elephantiasis of the lower legs in tropical Africa. Trop Geogr Med 36:1–5

Price R, Gaber BP, Lvov Y (2001) In vitro release characteristics of tetracycline HCI, khellin and nicotinamide adenine dinucleotide from halloysite, a cylindrical mineral. J Microencapsul 18:713–722

Quintela A, Terroso D, Almeida Salome FP, Reis P, Moura A, Correira A, Ferreira da Silva E, Forjaz V, Rocha F (2010) Geochemical and microbiological characterization of some Azorean volcanic muds after maturation. Res J Chem Environ 14:66–74

Quintela A, Terroso D, da Silva EF, Rocha F (2012) Certification and quality criteria of peloids used for therapeutic purposes. Clay Miner 47:441–451

Quintela A, Terroso D, Costa C, Sá H, Nunes JC (2015) Rocha F (2015) characterization and evaluation of hydrothermally influenced clayey sediments from Caldeiras da Ribeira Grande fumarolic field (Azores archipelago, Portugal) used for aesthetic and pelotherapy purposes. Environ Earth Sci 73:2833–2842. https://doi.org/10.1007/s12665-014-3438-8

Rabea EI, Badawy ME, Stevens CV et al (2003) Chitosan as antimicrobial agent: applications and mode of action. Biomacromolecules 4(6):1457–1465

Rambaud A (1989) Les boues thermales. In: Chr H (ed) Crénotherapie et Réadaptation. Masson, Paris, pp 9–19

Rambaud A, Rambaud J, Berger G, Pauvert B (1986) Mesure et étude du comportement thermique des boues thermales. J Fr Hydrol 17:392–302

Rautureau M, Liewig N, Gomes CSF, Katouzian-Safadi M (2010) Argiles et Santé : Propriétés et Thérapies. Editions Médicales Internationales. Lavoisier, 184 pp. ISBN 978-2-7430-1202-1

Rautureau M, Gomes CSF, Liewig N, Katouzian-Safadi M (2017) Clays and health: properties and therapeutic uses. Springer, Cham. ISBN: 978-3-319-42883-3

Rautureau M, Liewig N, Gomes CSF, Katouzian-Safadi M (2017) Clays and health: properties and therapeutic uses. Springer, Cham , 217pp. ISBN 978-3-319-42883-3. https://doi.org/10.1007/978-3-319-42884-0

Reichardt F (2008) Ingestion d'argile spontanée chez le rat: rôle dans la physiologie intestinale, Thèse, Université Louis Pasteur, Strasbourg

Reid R (1992) Cultural and medical perspectives on geophagia. Med Anthropol 13:337–351

Reilly C, Henry J (2000) Geophagia: why do humans consume soil? Nutr Bull 25:141–144

Reinbacher R (2003) Healing Earths: the third leg of medicine. 1st Books Library, Bloomington, 244 pp

Rondanelli M, Opizzi A, Perna S, Faliva MA, Buonocore D, Pezzoni G, Michelotti A, Marchetti R, Marzatico F (2012) Significant two-weeks clinical efficacy of an association between Massaciuccoli peat and sodium chloride water of Undulna Thermae measured on gynoid lipodystrophy in a group of overweight-female. Ann Ig 24(5):369–378

Roques CF (2004) Mud therapy and health, proceedings of the 3rd symposium on thermal muds in Europe. Dax:75–77

Roques CF (2015) Mud-therapy: data for clinical evidence. Balnea 10:57–62

Rosenblat A (1964) Los otomacos y taparitas de los llanos de Venezuela. Estudio etnográfico y lingüístico. Instituto de antropología e historia, Tomo I

Ross M, Nolan RP, Langer AM, Cooper WC (1993) Health effects of mineral dusts other than asbestos. In: Guthrie GD, Mossman BT (eds) Health effects of mineral dusts. Reviews in mineralogy, vol 8. Mineralogical Society of America, Washington, DC, pp 361–407

Rossainz-Castro LG, De la Rosa-Gomez I, Olguín MT, Alcantara-Diaz D (2016) Comparison between silver-and copper-modified zeolite-rich tuffs as microbicidal agents for *Escherichia coli* and *Candida albicans*. J Environ Manag 183:763–770. https://doi.org/10.1016/j.jenvman.2016.09.034

Rossi D, Jobstraibizer PG, Dal Bosco C, Bettero A (2013) A combined chemico-mineralogical and tensiometric approach for evaluation of Euganean Thermal Mud (ETM) quality. J Adhes Sci Technol 27:30–45

Roudsari MR, Karimi R, Sohrabvandi S, Mortazavian AM (2015) Health effects of probiotics on the skin. Crit Rev Food Sci Nutr 55:1219–1240

Rovira B, Gaitán F (2010) Los búcaros: de las Indias para el mundo. Canto Rodado 5:39–78

Rowe JH (1946) Inca culture at the time of the Spanish conquet. In: Steward J (ed) The Andean civilizations, vol 143 (2). Bur Am Ethnol Washington DC, Bull, pp 183–330

Ruiz-Hitsky E, Darder M, Alcântara A, Wicklein B, Aranda P (2015) Recent advances on fibrous Cla-based nanocomposites. Adv Polym Sci 267:39–86

Saathoff E, Olsen A, Kvalsvig JD, Geissler PW (2002) Geophagy and its association with geohelminth infections in rural school children from northern KwaZulu Natal, South Africa. Trans R Soc Trop Med Hyg 96:485–490

San Martin Bacaicoa J (1994) Peloides en general: Características físicas, efectos biológicos e indicaciones terapéuticas. In: Armijo M, San Martin J (eds) Curas balneárias y climáticas, Talasoterapia y Helioterapia. Complutense, Madrid, pp 315–331

Sanchez CJ, Parras J, Carretero MI (2002) The effect of maturation upon mineralogical and physicochemical properties of illitic-smectitic clays for pelotherapy. Clay Miner 37:457–463

Sandri G, Bonferoni MC, Ferrari F, Rossi S, Aguzzi C, Mori M, Caramella C (2014) Montmorillonite-chitosan-silver sulfadiazine nanocomposites for topical treatment of chronic skin lesions: in vitro biocompatibility, antibacterial efficacy and gap closure cell motility properties. Carbohydr Polym 102:970–977

Sandri G, Bonferoni MC, Rossi S, Ferrari F, Aguzzi C, Viseras C, Caramella C (2016) Clay minerals for tissue regeneration, repair, and engineering. In: Ågren MS (ed) Wound healing biomaterial. Elsevier, pp 385–402

Sandri G, Aguzzi C, Rossi S, Bonferoni MC, Bruni G, Boselli C, Ferrari F (2017) Halloysite and chitosan oligosaccharide nanocomposite for wound healing. Acta Biomater 57:216–224

Santaren J, Alvarez A (1994) Assessment of the health effects of mineral dusts: the sepiolite case. Indus Mineral 101-117, April

Santos D, Silva JBP, Estanqueiro M, Gomes CSF, Sousa Lobo JM (2014) Research and development of cosmetic and medical peloids using geomaterials and biomaterials. Bol Soc Esp Hidrol Méd 29(2):230–231

Sarsan A, Akkaya N, Ozgen M, Yildiz N, Atalay NS, Ardic F (2012) Comparing the efficacy of mature mud pack and hot pack treatments for knee osteoarthritis. J Back Musculoskelet Rehabil 25(3):193–199

Saunders C, Padilha PC, Della LB et al (2009) Pica: epidemiology and association with pregnancy complications [in Portuguese]. Rev Bras Ginecol Obstet 31:440–446

Sawai J (2003) Quantitative evaluation of antibacterial activities of metallic oxide powders (ZnO, MgO, CaO) by conductimetric assay. J Microbiol Methods 54:177–182

Schaefer H, Redelmeir TE (1996) Skin barrier: principles of Percutaneous Absorption. Karger S (ed), Zurich, Switzerland

Schmidt-Malan SM, Caflisch KM, Mandrakar JN, Williams LB, Patel R (2018) Activity of antibacterial clay against drug-resistant bacteria. Abstracts of the Annual Meeting of the Clay Minerals Society

Schnetz E, Fartasch M (2002) Microanalysis for the evaluation of penetration through the human skin barrier: a promising tool for future research? Eur J Pharm Sci 12:165–174

Schruazer GN, Shrestha KP (1990) Lithium in drinking water and the incidences of crimes, suicide and arrests related to drug addiction. Biol Trace Elem Res 25:105–113

Serofilli A (1994) La Fango - Balneoterapia. PICCIN, Padova, 130 pp

Seseña N (1991) El búcaro de las Meninas. Velazquez y la arte de su tiempo. V Jornadas de Arte. C.S.I.C., pp 171−180

Seseña N (2009) El vicio del barro. Ed. El Viso, Madrid

Sharma S, Grewal S, Vakhlu J (2018) Phylogenetic diversity and metabolic potential of natural healing clay: evidence for the role of clay microbes in skin disease management. Arch Microbiol

Sheppard SC (1998) Geophagy: who eats the soils and where do possible contaminants go? Environ Geol 33:109–114

Shinondo C, Mwikuma G (2009) Geophagy as a risk factor for helminth infections in pregnant women in Lusaka, Zambia. Med J Zambia 35:48–52

Silva JBP, Santos D, Amaral MH, Ramos P, Franco A, Gomes CSF, Lobo JM (2015) Casos de estudo de tratamento de patologia mamária com peloide terapêutico. Balnea 10:120–122

Sizaire V, Nackers F, Comte E, Portaels F (2006) Mycobacterium ulcerans infection: control, diagnosis, and treatment. Lancet Infect Dis 6(5):288–296

Soria CO, Vela ML, Jalil MER (2018) "Copahue: La Ciencia, Lo Magico y El Arte de Curar". Repositorio Relibro, Universidad Nacional del Comahue, 170pp. ISBN 978-987-783-027-9

Spilioti E, Vargiami M, Letsiou S, Gardikis K, Sygouni V, Koutsoukos P, Chinou I, Kassi E, Moutsatsou P (2017) Biological properties of mud extracts derived from various spa resorts. Environ Geochem Health 39:821–833

Steinstand S (2012) Transdermal delivery of water-soluble molecules into human skin MSc thesis, Norwegian University of Science and Technology (NTNU), Trondheim, 131pp

Stokes T (2006) The earth eaters. Nature 444(30):543–544

Suárez M, González P, Dominguez R, Bravo A, Melián C, Perez M (2011) Identification of organic compounds in San Diego de los Baños peloid (Pinar del Rio, Cuba). J Altern Complement Med 17(2):155–165

Sugawara N, Yaui-Furukori N, Ishii N, Iwata N, Terao T (2013) Lithium in tap water and suicide mortality in Japan. Int J Environ Res Public Health 10(11):6044–6048

Summa V, Tateo F (1999) Geochemistry of two peats suitable for medical uses and their behaviour during leaching. Appl Clay Sci 15:477–489

Suresh R, Borkar SN, Sawant VA, Shende VS, Dimble SK (2010) Nanoclay drug delivery systems. Int J Pharm Sci Nanotechnol 3(2):901–905

Svensson SL, Behroozian S, Xu W, Surette MG, Li L, Davies J (2017) Kisameet glacial clay: An unexpected source of bacterial. Diversity 8(3):e00590–e00517

Syafawani N, Nizam NA, Chun C (2016) Antimicrobial activity of copper-kaolinite and surfactant modified copper-kaolinite against gram-positive and gram-negative bacteria. Jurnal Teknologi (Sciences and Engineering) 76(3–2):127–132

Tan J, Zhu W, Wang W, Li R, Hou S, Wang D, Yang L (2002) Selenium in soil and endemic diseases in China. Sci Total Environ 284:227–235

Tanojo H, Boelsma E, Junginger H, Ponec M, Boddé H (1999) In vivo human skin permeability enhancement by oleic acid: a laser Doppler velocimetry study. J Control Release 58:97–104

Tateo F, Summa V (2007) Element mobility in clays for healing use. Appl Clay Sci 36:64–76

Tateo F, Summa V, Bonelli GC, Bentivenga G (2001) Mineralogy and geochemistry of herbalist's clays for internal use: simulation of the digestive process. Appl Clay Sci 20:97–109

Tateo F, Summa V, Gianossi ML, Ferraro G (2006) Healing clays: mineralogical and geochemical constraints on the preparation of clay-water suspension ("argillic water"). Appl Clay Sci 33:181–194

Tateo F, Ravaglioli A, Andreoli C, Bonina F, Coiro V, Degetto S, Giaretta A, Menconi Orsini A, Puglia C, Summa V (2009) The in vitro percutaneous migration of chemical elements from a thermal mud for healing use. Appl Clay Sci 44:83–94

Tayie F (2004) Pica: motivating factors and health issues. Afr J Food Agric Nutr Dev 4(1) http://www.bioline.org.br/request?nd04010

Tefner IK (2014) Effects of balneotherapy on musculoskeletal disorders with chronic pain, PhD thesis, Univ. Szeged, Hungary, 80 pp

Teixeira F (2015) Da peloterapia tradicional à peloterapia científica. Balnea 10:63–81

Teixeira F, Maraver F, Crespo PV, Campos A (1996) Estudo microanalítico da materia orgánica de águas sulfúreas portuguesas e espanholas. Pub Inst Clim Hidrol da Univ de Coimbra 34, 1–5

Tejero Garcia P (2014) Peloterapia en cosmetica y medicina estética. In: Peloterapia: Aplicaciones médicas y cosméticas de fangos termales. 185–190, Hernandez Torres A (coordinador), Fundación Bilbilis, Madrid

Tenti S, Cheleschi S, Galeazzi M, Fioravanti A (2014) Spa therapy: can bea valid option for treating knee osteoarthritis? Int J Biometeorol. https://doi.org/10.1007/s00484-014-0913-6.5

Thomson CD (2003) Selenium physiology. In: Encyclopedia of food science and nutrition, 2nd edn

Tolomio C, Ceschi-Berrini C, Moschin E, Galzigna L (1999) Colonization by diatoms and antirheumatic activity of thermal mud. Cell Biochem Funct 17(1):29–33

Tolomio C, Berrini CC, De Appolonia F, Galzigna L, Masiero L, Moro I, Moscin E (2002) Diatoms in the thermal mud of Abano Terme, Italy (maturation period). Arch Hydrobiol Algol Stud 143:11–27

Tolomio C, De Appolonia F, Moro I, Berrini CC (2004) Thermophilic microalgae growth on different substrates and at different temperature in experimental tanks in Abano Terme (Italy). Algol Stud 111:145–157

Tong G, Yulong M, Peng G, Zirong X (2005) Antibacterial effects of the Cu(II)-exchanged montmorillonite on *Escherichia coli* K88 and *Salmonella choleraesuis*. Vet Microbiol 105:113–122

Top A, Ulku S (2004) Silver, zinc, and copper exchange in a Na-clinoptilolite and resulting effect on antibacterial activity. Appl Clay Sci 27:13–19. https://doi.org/10.1016/j.clay.2003.12.002

Torrella F (2006) La sulfuraria de Baños de Montemayor (Cáceres): características morfológicas y funcionales de la comunidad microbiana constituyente. An Hidrol Med 1:61–78

Tricás JM, Fortún M, Jiménez S, Estébanes E (2014) Fisioterapia: fundamentación fisioterápica de la utilización de peloides. In: Hernandez A (coord.). Peloterapia: aplicaciones médicas y cosméticas de fangos termales, Madrid, Fundación Bilbilis, 251–260

Trivedi TH, Daga GL, Yeolekar ME (2005) Geophagia leading to hypokalemic quadriparesis in a postpartum patient. J Assoc Physicians India 53:205–207

Tsegay G, Tamiru A, Amberbir T et al (2016) Willingness to pay for footwear, and associated factors related to podoconiosis in northern Ethiopia. Int Health:345–353

Tserenpil S, Dolman G, Voronkov MG (2010) Organic matters in healing muds from Mongolia. Appl Clay Sci 49(1–2):55–63

Tully J, Yendluri R, Lvov Y (2016) Clay nanotubes for enzyme immobilization. Biomacromolecules 17:615–621

Turpin J (2004) Baked clay balls and earth ovens in south Central Texas. Curr Archeol Texas 6(2):9–14. https://www.thc.state.tx.us/archeology/aapdfs/CAT_Nov_04.pdf

Ubogui J, Rodríguez-Lupo L, Ficoseco H, Sevinsky L, Kien K, Stengel F (1991) Terapéutica no convencional de la Psoriasis en las termas de Copahue (Neuquén Argentina). Experiencia preliminar. Arch Arg Dermatol 41:25–39

Ubogui J, Stengel FM, Kien MC, Sevinsky L, Rodríguez Lupo L (1998) Thermalism in argentine: alternative or complementary dermatologic therapy. Arch Dermatol 134(11):1411–1412

Untura M, De Michele D, Giacomino M, Belderrain A (2007) Niveles plasmáticos de interleukina 1- β, cortisol, 17- β estradiol y ESG tras fangoterapia y fisioterapia en mujeres postmenopáusicas con artrosis. An Hidrol Med 2:65–74

Unuabonah EI, Taubert A (2014) Clay-polymer nanocomposites (CPNs): adsorbents of the future for water treatment. Appl Clay Sci 99:83–92

Unuabonaha EI, Ugwujaa CG, Omorogiea MO, Adewuyia A, Oladojab NA (2018) Clays for efficient disinfection of Bacteria in water. Appl Clay Sci 151:211–223

Vaht M, Birkenfeldt R, Ubner M (2008) An evaluation of the effect of differing lengths of spa therapy upon patients with osteoarthritis (OA). Complement Ther Clin Pract 14:60–64

Valencia HC, Fernández NJ, Londoño SC, Cucunubá Z, Reyes HP, Lopez PM (2008, 2008) Geological influences on the soil, contributions to infections transmitted by helminths in Colombia. In: Proceedings of the international geological congress, vol 33, Oslo

Varga C (2010) Problems with classification of spa waters used in balneology. Health 2(11):1260–1263. https://doi.org/10.4236/health.2010.211187

Varga C (2016) On the proper study design applicable to experimental balneology. Int J Biometeorol 60:1307–1309. https://doi.org/10.1007/s00484-015-1113-8

Velasco MVR, Zague V, Dario M, Nishikawa DO, Pinto C, Almeida MM, Tossini G, Vieira-Coelho A, Baby AR (2016) Characterization and short-term clinical study of clay facial mask. Rev Ciencias Farmaceuticas Básica e Aplicada 37(1)

Valenzuela AD (1967) Comer terra. Boletín Cultural y Bibliográfico 10(7):1529–1540

Veniale F (1998) Applicazioni e utilizzazioni medico-sanitarie di materiali argillosi (naturali e modificati). Corso di Specializzazione, Gruppo Italiano AIPEA, pp 1–40

Veniale F (editor) (1999) Argille curative per fanghi peloidi termali e per trattamienti dermatologici e cosmetici. Symp.Gruppo Ital. AIPEA, Montecatini Terme/PT, Miner. Petrogr. Acta, v. XLII, 261–335

Veniale F (2007) Applicazioni e utilizzazioni medico-sanitarie di material argillosi naturali e modificati. In: Morandi N, Dondi M (eds) Argille e minerali delle argille. Guida alla definizione di caratteristiche e proprietà per gli usi industriali. Corso di Formazione, Gruppo Italiano AIPEA, Rimini, pp 205–239

Veniale F (ed.) (1996) Atti di Convegno Argille Curative. Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física. Gruppo Italiano AIPEA Salice Terme/PV, 145 pp

Veniale F, Barberis E, Carcangiu G, Morandi N, Setti M, Tamanini M, Tessier D (2004) Formulation of muds for pelotherapy: effects of "maturation" by different mineral waters. Appl Clay Sci 25:135–148

Veniale F, Bettero A, Jobstraibizer P, Setti M (2007) Thermal muds: perspectives of innovation. Appl Clay Sci 36:141–147

Vergaro V, Lvov YM, Leporatti S (2012) Halloysite clay nanotubes for *resveratrol* delivery in cancer cells. Macromol Biosci 12(9):1265–1271

Vermeer DE (1986) Geophagy in the American south. Bull Shreveport Med Soc 37:38

Vermeer DE, Ferrell RE Jr (1985) Nigerian geophagical clay: a traditional anti-diarrheal pharmaceutical. Science 227:634–636

Vermeer DE, Frate DA (1979) Geophagia in rural Mississippi: environmental and cultural contexts and nutritional implications. Am J Clin Nutr 32(10):2129–2135

Vincevica-Gaile Z, Stankevica K (2018) Impact of micro- and macroelement content on potential use of freshwater sediments (gyttja) derived from lakes of eastern Latvia. Environ Geochem Health 40:1725–1738. https://doi.org/10.1007/s10653-017-9912-y

Viseras C, López-Galindo A (1999) Pharmaceutical applications of some Spanish clays (sepiolite, palygorskite, bentonite): some pre-formulation studies. Appl Clay Sci 14:69–82

Viseras C, Cultrone G, Cerezo P, Aguzzi C, Baschini M, Valle J, Lopez-Galindo A (2006) Characterization of northern Patagonian bentonites for pharmaceutical uses. Appl Clay Sci 31:272–281

Viseras C, Aguzzi C, Cerezo P, Lopez-Galindo A (2007) Uses of clay minerals in semisolid health care and therapeutic products. Appl Clay Sci 36:37–50

Viseras C, Aguzzi C, Cerezo P, Bedmar MC (2008) Biopolymer–clay nanocomposites for controlled drug delivery. Mater Sci Technol 24:1020–1026

Viseras C, Cerezo P, Sanchez R, Salcedo I, Aguzzi C (2010) Current challenges in clay minerals for drug deliver. Appl Clay Sci 48:291–295

Viseras C, Aguzzi C, Cerezo P (2015) Medical and health applications of natural mineral nanotubes. In: Natural mineral nanotubes: properties and applications. Apple Academic Press, Oakville/Waretown, pp 437–448

Viseras C, Carazo E, Borrego-Sánchez A, Garcia-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C (2019) Clay minerals in skin drug delivery. Clay Clay Miner. https://doi.org/10.1007/s42860-018-0003-7

Vreca P, Dolenec T (2005) Biogeochemical estimation of copper contamination in the healing mud from Makirina Bay. Central Adriatic Environ Int 31:53–61

Wagner JC, McConnochie K, Gibbs AR, Pooley FD (1998) Chapter 7: Clay minerals and health. In: Parker et al (eds) Environmental interactions of clays. Springer, Berlin

Wang X, Dong H, Zeng Q, Xia Q, Zhang L, Zhou Z (2017) Reduced iron-containing clay minerals as antibacterial agents. Environ Sci Technol 51:2401–2408

Welsh J (2011) Dirty truth: humans eat dirt to shield the stomach. Retrieved from Live Science: https://www.livescience.com/14463-humans-eating-dirt-stomachs.html

WHO (2005) Bentonite, kaolin and selected clay minerals, Environmental health criteria 231. IPCS (International Program of Chemical Safety

WHO (2011) Guidelines for drinking water quality, 4th edn. WHO, Geneva

Wigler I, Elkayam O, Paran D, Yaron M (1995) Spa therapy for gonarthrosis: a prospective study. Rheumatol Int 15(2):65–68

Wiley AS, Katz SH (1998) Geophagy in pregnancy: a test of a hypothesis. Curr Anthropol 39:532–545

Wilkinson JB, Moore R (1982) Face packs and masks. In: Wilkinson JB, Moore RJ (eds) Harry's cosmeticology, 7th edn. Longman Group, London

Williams LB (2011) Antibacterial clays and their potential for medicinal applications. GeoMed2011, 4th International Conference on Medical Geology, Book of Abstracts, III-IV
Williams LB (2017) Geomimicry: harnessing the antibacterial action of clays. Clay Miner 52:1–24
Williams LB, Haydel SE (2010) Evaluation of the medicinal use of clay minerals as antibacterial agents. Inst Geol Rev 52:745–770
Williams LB, Hillier S (2014) Kaolins and health: from first grade to first aid. Elements 10:207–211
Williams LB, Holland M, Eberl DD, Brunet T, De Courrsou LB (2004) Killer clays! Natural antibacterial clay minerals. Mineral Soc Bull:3–8
Williams LB, Haydel SE, Giese R, Eberl DD (2008) Chemical and mineralogical characteristics of French green clays used for healing. Clay Clay Miner 56:437–452
Williams LB, Haydel SE, Ferrell R (2009) Bentonite, Bandaids and Borborygmi. Elements 5:99–104
Williams LB, Metge D, Eberl DD, Harvey R, Turner A, Prapaipong P, Poret-Peterson A (2011) What makes natural clay antibacterial? Environ Sci Technol 45:3768–3773
Wilson MJ (2003) Clay mineralogical and related characteristics of geophagic materials. J Chem Ecol 29:1525–1547
Wilson I, Keeling J (2016) Global occurrences, geology and characteristics of tubular halloysite deposits. Clay Miner 51(3):309–324
Wittman W, Fellingham SA (1970) Unusual hip disease in remote part of Zululand. Lancet 1:842–843
Worrall WE (1975) Clays and ceramic raw materials. Applied Science Publishers Ltd, London, 203pp
Woywodt A, Kiss A (1999) Perforation of the sigmoid colon due to geophagia. Arch Surg, Chicago 134:88–89
Woywodt A, Kiss A (2002) Geophagia: the history of earth-eating. J R Soc Med 95:143–146
Xu J, Campbell JM, Zhang N, Hickey W, Sahai N (2012) Did mineral surface chemistry and toxicity contribute to evolution of microbial extracellular polymeric substances? Astrobiology 12(8):785–798
Ye Y, Zhou YH, Xia MS, Hu CH, Ling HF (2003) A new type of inorganic antibacterial material: Cu-bearing montmorillonite and discussion on its mechanism. J Inorg Mater 18:569–574
Young SL (2010) Pica in pregnancy: new ideas about an old condition. Annu Rev Nutr 30:403–422
Young SL (2011) Craving earth. Columbia University Press, New York, 228 pp
Young SL, Wilson MJ, Miller D, Hillier S (2008) Toward a comprehensive approach to the collection and analysis of pica substances, with emphasis on geophagic materials. PLoS One 3:e3147
Young SL, Wilson MJ, Hillier S, Delbos E, Ali SM, Stolzfus R (2010a) Differences and commonalities in physical, chemical, and mineralogical properties of Zanzibari geophagic soils. J Chem Ecol 36:129–140
Young SL, Khalfan SS, Farag TH, Kavle JA, Ali SM, Hajji H, Rasmussen KM, Pelto GH, Tielsch JM, Stoltzfus RJ (2010b) Association of Pica with Anemia and gastrointestinal distress among pregnant women in Zanzibar, Tanzania. Am J Trop Med Hyg 83(1):144–151
Yuan P, Tan D, Bergaya F (2015) Properties and applications of halloysite nanotubes: recent research advances and future prospects. Appl Clay Sci 112–113:75–93
Yücesoy H, Geçmen I, Adıgüzel T, Karagülle M, Karagülle MZ (2019) Efficacy of balneological outpatient treatment (hydrotherapy and peloidotherapy) for the management of chronic low back pain: a retrospective study. Int J Biometeorol 63:351–357
Yuen JWM, Chung TWK, Loke AY (2015) Methicillin-resistant *Staphylococcus aureus* (MRSA) contamination in bedside surfaces of a hospital ward and the potential effectiveness of enhanced disinfection with an antimicrobial polymer surfactant. Int J Environ Res Public Health 12:3026–3041
Yvon J, Ferrand T (1996) Preparation ex-situ de peloids: Proprietés thermiques, mécaniques et d'échanges. Proc. Meeting "Argille Curative", Salice Terme/PV, Gruppo Ital. AIPEA, 67–74

Zague V, Almeida Silva D, Baby AR, Kaneko TM, Velasco MVR (2008) Clay facial masks: physicochemical stability at different storage temperatures. J Cosmet Sci 29(6):488–489. https://doi.org/10.1111/j.1468-2494.2007.00391_5.x

Zarate-Reyes L, López-Pacheco C, Nieto-Camacho A, Palacios E, López-Vidales V, Kaufhold S, Ufer K, Garcia-Zepeda E, Cervini-Silva J (2017a) Antibacterial clay against gram-negative antibiotic resistant bacteria. J Hazard Mater 342:625–632

Zarate-Reyes L, López-Pacheco C, Nieto-Camacho A, Apán MTR, Palacios E, López-Vidales V, Kaufhold S, Ufer K, Garcia-Zepeda E, Cervini-Silva J (2017b) Naturally occurring layered-mineral magnesium as a bactericidal against *Escherichia coli*. Appl Clay Sci 149:87–96

Zatta P, Kiss T, Suwalsky M, Berthon G (2002) Aluminium (III) as a promoter of cellular oxidation. Coord Chem Rev 228(2):271–284

Zhang BJ, Yang LS, Wang WY et al (2010) Quantification and comparison of soil elements in the Tibetan Plateau Kashin-Beck disease area. Biol Trace Elem Res 138(1–3):68–78

Zhang BJ, Yang LS, Wang WY et al (2011) Environmental selenium in the Kaschin–Beck disease area, Tibetan Plateau, China. Environ Geochem Health 33(5):495–501

Zhou H, Wang T, Li Q, Li D (2018) Prevention of Keshan disease by selenium supplementation: a systematic review and meta-analysis. Biol Trace Elem Res 186:98–105

Ziegler JL (1997) Geophagy: a vestige of paleonutrition. Tropical Med Int Health 2:609–611

Chapter 8
Minerals and the Origin of Life

Celso S. F. Gomes and Michel Rautureau

Abstract Since ancient times, philosophers and scientists have sought to unravel the origins of life on Earth. The identification of the environment, of the natural physicochemical conditions, and how the primitive forms of life emerged and evolved still remains to be discovered. The chapter, based on the available scientific literature, identifies and discusses five main prevailing hypotheses for the origins of life on Earth based on more or less elaborated data: extraterrestrial or panspermia hypothesis (with origin and transport in meteorites and comets); clay hypothesis; submarine volcanic chimney or vent hypothesis; terrestrial hot spring hypothesis; and serpentinization hypothesis. In all the hypotheses referred to minerals, clay minerals and metal sulfide minerals in particular would have played decisive roles. As a matter of fact, minerals represent challenging substrates for life, since they are sources of nutrients and energy for prokaryotes (bacteria and archaea), single-celled organisms, to appear and evolve. The chapter ends mentioning that research goes on and expectations are high regarding the better understanding of the origin of both the solar system and life on Earth. Scientists hope to get relevant information from the very recent sample collected on the carbon-rich rocky Bennu asteroid by NASA's OSIRIS-REx probe.

8.1 Background Data

What is life? So far, the definition of life has not yet received a common acceptance within scientists, even for the simplest possible form of life exemplified by bacteria.

The Austrian physicist, Nobel Prize in Physics winner, Erwin Schrödinger (1887–1961), co-author of the quantum theory, had published in 1944 a book

---

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit “GeoBioTec”, University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

M. Rautureau
Docteur d'État ès Sciences Physiques, Retired of University of Orléans, Orléans, France

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_8

entitled *Life, Spirit and Matter*, where the author states that all life phenomena, hereditariety included, were the result of physicochemical phenomena and laws. Despite the incapacity of both physics and chemistry to explain the life phenomena, there was no reason, according to the author, to doubt that they could be explained in the near future. The statement that life is both physical and chemical still is maintained valid. The new advances in biology, some of great impact, as is the case of genome sequencing in 2000 following the discovery, applying physics methods, of the molecular structure of DNA, in 1953, by the English physicist Francis Crick and the North American biologist James Watson, are giving justification to Schrödinger's statement. Presently, we well know that all living beings can be described by their genetic code just composed of four letters: A (adenine), T (thymine), G (guanine), and C (cytosine). It is interesting to mention that in the book referred to, Erwin Schrödinger made the comparison between the mineral (solid, inorganic, and crystalline) and the living organism, both multiatomic natural beings, the mineral behaving like a tridimensional and triperiodical crystal and the living organism behaving like an aperiodical crystal. In terms of statistical structure from a physicist's point of view, the living organism's tetradimensional structure is very much complex and fascinating than the mineral one. The living organism structure is determined by the structure of the egg cell after being fecundated, which is determined too by the structure of its nucleus, more precisely by the structure of its chromosomes, the material that supports and transmits life.

Arrhenius 2003 states that life entails a decrease of entropy and creation of order similarly to what happens in the formation of minerals or crystals. In contrast to the unlimited evolutionary possibilities for biomolecular systems the evolution in crystals is very much limited to changes in the distribution of structural defects including isomorphous atomic substitution. However greater changes are offered by hybrid systems minerals/organic molecules, minerals being able to concentrate and catalytically transforming organic molecules toward biofunctionality, situation well exemplified by the so-called Green Rust (GR) anionic clay minerals (Duval et al. 2019, 2020).

Erwin Schrödinger was somehow disappointed with the incapacity of physics to explain and understand life, comparatively to the contribution of biology, organic chemistry, biochemistry, and biotechnology. Very recently the Nobel Prize in Chemistry of 2020 went to *the rewriting of the code of life* by the French microbiologist Emmanuelle Charpentier and the American biochemist Jennifer Doudna. Both scientists have discovered the so-called genetic scissors CRISPR/Cas9 essential to directly manipulate or rewrite the DNA, the code of life, using a simple and precise technology that enables to cut the DNA in specific sites with the help of a very small molecule of RNA, the tracrRNA. From now on scientists are able to modify the DNA of animals, plants, and microorganisms, using a technology that represents a great revolution in the field of life sciences, in particular for its contribution for the development of new therapies for cancer and hereditarian diseases, although it could withdraw serious ethical questions.

Science made great advances, but questions remain unsolved about life definition and life origin or origins. According to Brack (2007), in a workshop held in Modena, Italy, in 2003, each member of the International Society for the Study of the Origins of Life was asked to give a definition of life, and 78 (seventy-eight) different answers were obtained occupying 40 (forty) pages of the workshop proceedings.

Since ancient times, philosophers and scientists have sought to unravel the origin of life on Earth. In ancient Greece, several philosophers with prominence for Aristotle (384–322 B.C.) reflected and wrote their ideas on the origin of life. For all these philosophers, life would come from *spontaneous generation* from inert or inanimate matter and from the interaction of four basic factors or raw materials: earth, air, water, and fire.

The thesis of *spontaneous generation* lasted for many centuries. It was not until the sixteenth century, in an initial experimental phase of science, particularly chemistry, physics, biology, and medicine, that the theory of the spontaneous generation of life began to be contradicted. With the instrument called the optical microscope, it began to be possible to observe minutely the living matter of small size and to identify the bacteria and cells.

The Italian physician Francesco Redi (1626–1697) owes the first and sustained criticism to the theory of spontaneous generation and, consequently, the formulation of the biogenic theory of life, later in 1860, well supported by the experiences of Louis Pasteur according to which all living beings have their origin from other living beings.

It is indeed due to the studies and experiments of Pasteur (1822–1895) in the fields of fermentation (studied wine fermentation and identified the microorganisms involved), pasteurization (through heat can be made sterilization, very useful in medicine), and vaccination (he discovered the attenuated forms of microorganisms that can be used to generate immunity) the total refutation of the theory of spontaneous generation and the bases for the development of modern science, because they allowed to answer two fundamental questions: Can matter organize itself? Can a living being exist without parents and grandparents? Not in either case, according to Pasteur, founder of chemistry and microbiology.

Notwithstanding all the knowledge then gained about the origin of life and the subsequent enormous and profound contribution of molecular and cellular biology and biochemistry as well as the theory of evolution of species due to the British naturalist Charles Darwin, it remains to be discovered in which environment, in what conditions, and how the primitive forms of life emerged and evolved. Despite the great diversity of living beings, from the simple bacteria to the highly complex man, Darwin, in 1859, had proposed their unification integrating them into one tree, the “tree of species evolution.”

In 1871 Darwin in a letter sent to his friend J.D. Hooker did suggest that life might have begun in a “Warm little pond with all sorts of ammonia, and phosphoric salts under the action of light, heat, electricity, and a protein compound was chemically formed, ready to undergo still more complex changes….” And about one century later, some scientists have proposed and tested the hypothesis of life beginnings in a *hot little cycling pool* which would have existed on volcanic land mass on the early Earth, more precisely in Hadean environments.

It is well known that living beings can be constituted, by a cell (prokaryotic beings that are cells without differentiated nuclei and eukaryotic beings that are cells where the genetic material is inside a differentiated nucleus) or by more cells (multicellular organisms whose cells perform different specific functions), the cell being the minimum unit, structural and functional.

There are three critical steps that lead toward cell formation:

1. Concentration of molecular components that participate in prebiotic reactions and control of water activity.
2. Stabilization and structural conformation of molecules.
3. Chemical evolution through complexification (Westall et al. 2018).

Bacteria were the earliest living organisms inhabiting the Earth, arising in the Archean and becoming dominant in the Proterozoic. The Earth formed about 4900 million years ago (4.9 Ga ago), and by 3800 million years ago (3.8 Ga ago), the first bacteria, living beings without nucleus such as the current bacteria, would have appeared.

Schoonen and Smirnov (2016) admit that the stage favorable for the origin of life may have been set during a period that was as short as 20 million years within the first 100 million years after the formation of the Moon (at ~4.5 Ga ago). The authors admit too that the Earth's atmosphere at that time contained more CO_2 (and N_2 and SO_2 too) than at any other period thereafter, a gas that by dissolution has turned the very warm ocean water (Zahnle (2006) estimates ocean water temperature within the range 60–110 °C) into a "seltzer" or carbonated water very acidic and aggressive to primitive crust minerals, and as the result of such water/mineral interaction, a range of organic compounds would had been formed through abiotic reactions, organic compounds that set the stage for the origin of life. The secondary minerals of rock weathering, clay minerals, zeolites, and released metals (e.g., Fe, Ni, and Mg) may have played a key role in setting the stage for life.

The first indications of life on Earth come from fossils, the colonial structures named *stromatolites*, the oldest known microfossils formed by photosynthesizing *cyanobacteria* and believed to be the last universal common ancestor (LUCA), found in the Archaean rocks from the Warrawoona formation, Western Australia, and dated back to 3.5 Ga ago (Schopf 1993). However, Manning et al. dated 3.86 Ga ago rocks containing traces of ancient life from the Akilia Island in West Greenland.

Lazcano and Miller (1994) put forward the following question: How long did it take for life to begin and evolve to cyanobacteria? Really, we don't know.

Only about 1800 Ga ago would have emerged nucleus cells (eukaryotes) that today form plants and animals.

Our planet was and still is the bacteria planet being also called the insect planet because 3/4 of all animals are insects. Among the bacteria, the so-called cyanobacteria, which are photosynthetic organisms, have been highlighted in the very distant past. They are supposed to play a relevant role in the history of life on Earth, providing the increase of oxygen content in the atmosphere. At present, *cyanobacteria* are directly responsible for almost half of the oxygen produced each year on Earth and, indirectly, for most of the rest. Ancestral forms of *cyanobacteria* would have evolved to form forms with chloroplasts, the cellular components responsible for photosynthesis in plants.

After the theory of spontaneous generation had been discredited, only religious explanations were offered to explain the origin of life.

The Russian biochemist Alexander Oparin, an atheist, disclosed in 1938 the results of studies developed and expounded on a theory called “prebiotic soup theory” which suggested that the origin of life on Earth could be explained by physicochemical reactions between the constituents of the primitive reductive atmosphere (carbon dioxide, nitrogen, and water) without oxygen, and the energy necessary for the effect may be due to:

1. Electrical discharges produced during storms.
2. Solar radiation.
3. Geothermal energy produced by volcanic activity.

Oparin studies were really published much earlier, already in 1924, in a book entitled *The Origin of Life* written in Russian.

In 1928 the British biologist J. Haldane without knowing Oparin’s studies speculated on the early earth conditions suitable for the emergence of life, subjecting a mixture of water, carbon dioxide, and ammonia to UV light.

From the experiences being carried out, the first simple organic molecules would had occurred on the surface of the warm water of the primitive oceans that would contain organic matter, the so-called primitive broth or primordial soup. Life would be the result of a process of transforming simple organic compounds (formed from inert matter) into complex, self-replicating organic compounds. Later researchers have argued that the concentration process of organic molecules could have occurred more effectively in seashore tidal pools rather than in bulk oceanic water (Bada and Lazcano 2002).

Bernal (1949) was the first researcher who conjectured that clay mineral surfaces were involved in the transformation process referred to. The importance of mineral surfaces to fix, select, and organize organic molecules was experimentally shown, using minerals such as graphite, molybdenite, calcite, and *clay minerals* by some researchers: and Hazen (2005).

About the importance of clay minerals on the emergence of life Cairns-Smith (1982, 1985) proposes that the emergence of life was not just promoted by a mineral, but that the first lifeform was perhaps a clay mineral itself. The author suggests that clay minerals carry a kind of genetic information in their complex sequences of point defects, layer orientations, and metal cation substitutions.

We well know the unique characteristics of clay minerals: the widespread occurrence at the Earth’s surface, in soil and water; the very small particle size; the platy and thin particle shape; the high content of structural defects (point, planar, and volumetric defects); the high content and diversity of water (hygroscopic, zeolitic, and structural); the high content and diversity of metals, some exchangeable cations; the high chemical reactivity; the high catalytic capacity; and the gregarious character of single or composite species.

The proof of Oparin's theory occurred with the experiments carried out by the American researchers Urey (1952) and Miller and Urey, who conceived an apparatus to realize an experiment carried out by Stanley Miller (1953), a young student of Harold Urey, in which the conditions prevailing in the atmosphere of the primitive earth were simulated.

A mixture of gases, methane, ammonia, hydrogen, and water was subjected to electric discharges of 60,000 volts representing lightning that would occur in the primitive atmosphere. The result of the experiment was the formation of black deposits on the sides of the vessel which constituted of simple organic molecules including acetic acid, glucose, and the amino acids glycine, alanine, glutamic acid, and aspartic acid, substances that cells use in protein synthesis. At the time this result was criticized because it did not demonstrate how the first cells appeared. However, Miller's publication really opened the field of experimental prebiotic chemistry.

According to Shapiro (2006), actually nucleic acids and proteins are essential constituents of modern cells and constitute much of their biomass.

The most widely held theories regarding the origin of life assume, in general, that life began with the spontaneous appearance of a large molecule like RNA that combines the genetic capabilities of nucleic acids with the catalytic abilities of proteins.

For authors such as Gilbert (1986) and Bada and Lazcano (2002), life did begin with an RNA world: "RNA molecules performing the catalytic activities necessary to assemble themselves from a nucleotide soup." However, such hypothesis does not explain how the first self-replicating RNA molecule was formed.

The abiotic formation of RNA is generally based on a process called prebiotoc synthesis, catalyzed by minerals such as clay minerals (Miller 1953; Miller and Orgel 1974; Ertem 2004).

The clay mineral montmorillonite has the interesting property of catalyzing the formation of RNA from its sub-units, the nucleotides (Wade 2003).

The issue of *Elements*, magazine of mineralogy, geochemistry, and petrology, entitled "Origins of Life: Transition from Geochemistry to Biogeochemistry," dated of December 2016, contains several articles from Sahai et al., Schoonen and Smirvov, Dalai et al., Maurel and Leclerc, Belmonte and Mansy, and Kee and Monnard, which highlight the roles of minerals and geochemical environments in the emergence of protocells, the cells that might have preceded "LUCA," the last universal common ancestor, i.e., the organism from which all living organisms today descend.

Lanier and Williams (2017) consider five models for the origin of life supported by distinct groups of researchers and each one leading to the "LUCA":

1. The *RNA world* model for which the privileged function is replication.
2. The *clay world* model for which the privileged function still is replication, clay and clay mineral surfaces, acting as catalysts.
3. The *metabolism-first world* model for which the privileged function is metabolism.
4. The *thermal-first world* model for which the privileged function is the harvesting of energy from chemical gradients.

5. The *membrane world* model for which the privileged function is compartmentalization.

The understanding of both origin and evolution of life indeed requires a multidisciplinary approach necessarily involving contributions from geoscientists, biologists, chemists, physicists, astrobiologists, astrophysicists, and geneticists.

The question of origin and evolution of life on Earth and elsewhere in the universe has ever been quite challenging. However, despite the so many attempts, studies, and proposals being carried out and disclosed in the last 70 years, the origin of life is still a big enigma. When, where, and how did life on Earth originate? These questions on the origin of life are among the biggest unsolved problems in natural sciences (Kitadi and Maruyama 2018).

In fact, scientists are still far from understanding the ancient and intricate processes that led to the origin of life, and fascinating experiences and theories will continue to contribute small pieces to the so immensely complex puzzle (Hazen 2005).

From the available scientific literature, we can say that five main prevailing hypotheses are known for the origin of life on Earth, based on more or less elaborated data:

1. Extraterrestrial or panspermia hypothesis (through meteorites and comets).
2. Clay hypothesis.
3. Submarine volcanic chimney or vent hypothesis.
4. Terrestrial hot spring hypothesis.
5. Serpentinization hypothesis.

In all the hypotheses referred to minerals, clay minerals and metal sulfide minerals, in particular, would have played decisive roles. As a matter of fact, minerals represent challenging substrates for life, since they are sources of nutrients and energy for prokaryotes (bacteria and archaea), single-celled organisms (Southam 2012).

The paleomineralogy of Earth prior to the origin and global distribution of life, i.e., the knowledge of the diversity and distribution of Hadean minerals, would be especially important for the creation and support of the models of life's origins (Morrison et al. 2018).

In all the five aforesaid hypotheses, life takes place or rises in water, and recently Li et al. (2018) state that metal sulfide minerals, abundant and quite diverse on Earth, could have been key players in prebiotic processes of various kinds, the abiotic synthesis of the basic building blocks requisite for metabolism and replication (Russell et al. 2003; Martin and Russell 2007; Cleaves et al. 2012; Kitadai and Maruyama 2018), acceptable in several scenarios, such as the "iron-sulfur world" model (Wächtershäuser 1988, 2007) and the "iron-sulfur membrane" model (Russell and Hall 1997, 2006).

Metal sulfides are ubiquitous in reducing environments, including, within others, deep-sea hydrothermal vent deposits, sulfide-rich euxinic sediment environments (e.g., Black Sea), and black shale. Deep-sea hydrothermal systems associated with

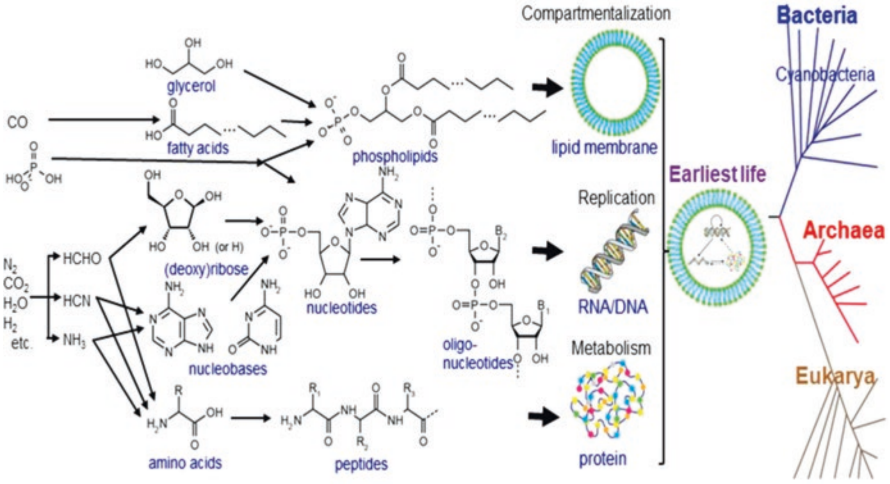


Fig. 8.1 Structures, components, and abiotic synthetic pathways of biomacromolecules operating three fundamental functions of life: replication, compartmentalization, and metabolism. (Source: Kitadai N and Maruyama S/Geoscience Frontiers 9, 1117–1153, 2018)

the serpentinization of ultramafic rocks are among the most plausible geological settings for life to have originated (Fig. 8.1).

Martinez and Mateo-Marti (2018) have shown that *pyrite* surface chemistry is highly sensitive to the chemical changes induced by UV irradiation. Surface chemical changes induced by UV help to increase the probability of adsorption of molecular species and their subsequent concentration on the *pyrite* crystal surfaces. *Pyrite*, FeS_2, is one of the most important and abundant sulfide minerals on Earth. Due to its catalytic activity, *pyrite* crystal surfaces would play an important role in heterogeneous catalysis (Liu et al. 2012, 2013) and a role in the origin of life and prebiotic chemistry (Saladino et al. 2008). The catalytic functions of sulfides have been poorly explored in the context of the origin of life.

Martinez and Mateo-Marti (2018) reckon that the complex prebiotic geochemical environment is still an enormous challenge. Natural transition metal sulfides exhibit large variations in chemical composition, crystal structure defects, and valence states of both components, metal and sulfur species. Such diversity among the available catalysts, clay minerals included, could have generated a large number of possible reactions, leading to the formation of complex prebiotic organic synthesis networks and ultimately autocatalytic reaction networks (Guttenberg et al. 2017; Tawfik 2010).

Defining life still is an intriguing and long-lasting question that has not yet received a commonly accepted answer. However, the various definitions have in common the following arguments: open chemical system capable of metabolic activity, self-replication, and evolving. Metabolism provides the energy and the basic building blocks to make DNA and other genetic materials, and genetics provides the necessary instructions to make hundreds of molecules essential to metabolism.

Origin-of-life researchers are engaged in an intense ongoing debate about whether metabolism and genetics arose simultaneously or independently, and if in the last situation which one came first (Orgel 1986).

8.2 Extraterrestrial Hypothesis

Life on Earth may have emerged shortly after the so-called heavy bombardment phase, perhaps as early as 3.90–3.85 Ga ago. Many scientists accept the hypothesis that ancient meteorites and comets being the source of a significant amount of water and organic molecules to early Earth would be responsible for the rise of life on our planet.

In the *extraterrestrial hypothesis* or *panspermia hypothesis*, there are scientists who admit, by the theory of panspermia, that life began with the first organisms (bacteria) coming from outer space of the Earth, through meteorites, carbonaceous meteorites. This is the case of the meteorite Allan Hills 84,001 or ALH84001 originating from Mars's crust that was shown by McKay et al. (1996) to bear microscopic structures resembling fossilized bacteria and a variety of organic molecules, including polycyclic aromatic hydrocarbons. It is also the case of Murchison's meteorite (crashed in Australia and found in 1969) that bears microstructures identified as fossilized bacteria by Kvenvolden et al. (1970) and in which traces of xanthine and uracil, precursors of the DNA and RNA molecules, have been identified. Organic compounds were first detected by Nagy et al. in Orgueil carbonaceous meteorite which fell to Earth in 1864, and since then more than 14,000 organic compounds, including 70 amino acids and other biologically important organic molecules, have been detected (Llorca 2004; Callahan et al. 2011). The name *panspermia* (from the Greek word meaning "all seeds") is due to Anaxagoras, a Greek philosopher who lived 2500 years ago.

Over the last 20 years, 30 meteorites have been found on our planet and assumed to be originated in Mars' crust. The main concept of panspermia is that life, or the fundamental building blocks or seeds of life, exist throughout the universe (Hoyle and Wickramsinghe 1977, 2000; Warmflash and Weiss 2005). Meteorites are divided into two categories based on chemical composition and texture: chondrites (which make up about 80%, which are believed to represent the most primitive materials in the solar system) and achondrites. In turn the chondrites comprise four classes, including one of them the carbonaceous chondrites or carbonaceous meteorites.

According to Martins (2011), carbonaceous meteorites contain a great variety of extraterrestrial organic compounds that may be the origin of the first prebiotic forms of life. In an article published in April (2014) in the scientific Journal *Geochimica et Cosmochimica Acta*, a team of researchers analyzed eight meteorites of the carbonaceous chondrite type in the Astrobiology Laboratory of the Goddard Center of NASA and identified in their interior concentrations of vitamin B3 that cannot be explained by contamination. Vitamin B3, so named as the third vitamin B to be discovered, corresponds to the compound $C_6H_5NO_2$ called *niacin* or *nicotinic acid* which is one of the essential nutrients for humans, playing an important role in cellular energy metabolism helping to release energy from the hydrates of carbon. The above investigation reinforces the thesis that life would not be a product entirely terrestrial. Some of the essential components of life would have come to Earth on board of "rocks" from space.

In the *extraterrestrial hypothesis*, the emergence of life may also have resulted from the impact of comets with planets such as Earth. This hypothesis arose in 2006 when NASA had analyzed the materials of the tail of comet 81P/Wild2 collected by the Stardust spacecraft probe, and organic compounds had been found, as was the case of the amino acid glycine, $C_2H_5O_2N$. Laboratory experiments were conducted later in the Universities of Berkeley, California, and Manoa, Hawaii, and in 2013 at the Imperial College in London by a team of British and American researchers led by the Portuguese astrobiologist Zita Martins. The researchers attempted to replicate the reported impact by firing high-speed steel projectiles (25,740 km/h) against an ice-cold mixture of composition assumed to be similar to that of comets, with water and simple carbon dioxide, methane, and ammonia molecules. The experiments showed that the breakdown and reorganization of organic molecules resulted in the formation of amino acids, the basic building blocks of living beings. And the experiments had continued in order to discover how of the amino acids can result the formation of proteins, and from these the formation of cells, the basic units of the life (see "Comets" issue n° 2 of *Elements*, April 2018).

Organic molecules and volatiles (e.g., H_2O, CO, and CO_2) are major building blocks of planets, as evidenced by the fact that their constituents (H, C, O, and S) are among the most abundant elements in the solar system, the first organic molecules and volatiles being produced in interstellar clouds through photochemical reactions in the gas phase and on dust surfaces (Yabuta et al. 2018).

Most researchers consider implausible the *panspermia hypothesis* based on the idea that the bacteria found on Earth would not survive the space conditions and the enormous impact of the asteroid on the planet. But it is possible that the entry into Earth's atmosphere would heat the meteorite surface but not the interior. The enthusiasts of the *panspermia hypothesis* consider that an ancestral form of life was delivered to Earth, but they do not theorize on the original source of that life form.

8.3 Clay Hypothesis

There are researchers who admit that the origin and evolution of life on Earth were catalyzed by minerals. In fact, several researchers consider that the prebiotic synthesis of primitive forms of life was catalyzed by minerals such as *pyrite* (FeS_2) and clay minerals (essential components of clays) suspended in the surface of the ocean, known as hydrous phyllosilicates whose crystals and particles of generally less than 2 μm (i.e., less than 0.002 mm) exhibit essentially lamellar forms and have a number of properties which are essentially due to the fact that they have a negative charge of varying degrees from species to species, with emphasis on catalyst properties.

Clay minerals exist in all terrestrial environments: earth, water (sweet and salty), and air. On Earth, as soil components, these as other minerals are a source of nutrients and/or energy, thus fundamental to the natural creation of life. And since the idea that life would have arisen in seawater, the clay minerals in suspension, known as its catalytic capacity due to the micrometric size, the lamellar form and the overall negative electric charge of its particles, would have been the support and promoter of the synthesis of biomolecules essential to life.

In the last 70 years, a significant number of researchers, particularly chemists, geologists, biologists, and physicists, have developed projects and achieved results pointing out for the role of clay and clay minerals on the emergence of life on Earth.

Oparin (1938) has suggested that the biological molecules that came together to form the first living thing were produced by natural chemical reactions. Oparin argued that a "primeval soup" rich in organic molecules could be created in an oxygen-deprived atmosphere, but rich in hydrogen, methane, and ammonia, through the action of sunlight.

Bernal (1949) suggested that polymerization may have occurred between biomolecules adsorbed on mineral surfaces. The author was the researcher who first suggested the key role of clay minerals in chemical evolution and the origins of life because due to their particle minuteness, particle platy shape, and particle electric charge (overall negatively charged sites overcomes the overall positively charged sites), they are the privileged minerals to host the polymerization of biomolecules.

In 1953, Stanley Miller, a student of Harold Urey, reported the formation of four amino acids (glycine, alanine, aspartic acid, and glutamic acid) by subjecting to electric discharges a mixture of methane, ammonia, hydrogen, and water. As a matter of fact, Miller's publication has been the ground for experimental prebiotic chemistry. For Miller and Urey (1959), the amino acid formation would have resulted from the action of sparks during thunderstorms which provided the energy source, and the required catalyst of chemical reactions would have been the ash glassy particles that projected into the air by volcanic activity which would had been deposited in the surface waters of seas and lakes and rapidly transformed into clay minerals.

Many other researchers have shown interest on the emergence of life on Earth proposing that minerals (clay minerals included) and chemical elements played a key role in the emergence of life by catalyzing the synthesis, after selection, protection, and concentration of the biomolecules essential to life (Bernal 1949; Goldschmidt 1952; Corliss et al. 1981; Cairns-Smith and Hartman 1986; Gilbert 1986; 2006; Holm 1992; Wächtersshäuser 1988, 1992; Lazcano and Miller 1994; Zubay 2000; Russell 2003; Bada 2004; Ertem 2004; Cairns-Smith 2002, 2005; Martin and Russell 2002; Ferris 2005; Pross 2004; Hazen 2005; Brack 2006; Meunier et al. 2010; Lambert 2015; Lanier and Williams 2017; Li et al. 2018).

Cairns-Smith (1982, 1985) and Cairns-Smith and Hartman (1986) particularly in the book of the last two authors referred to consider that replication and catalytic activity are the two most primitive features of a recognizable living system and discuss the role of clays as catalysts on the early Earth, Mars, and meteorites. Cairns-Smith was truly enthusiastic about the unique characteristics of clay minerals that include a kind of genetic information; for him clay minerals were indeed the first lifeforms on Earth. What is life? He demands. How can we distinguish the living from the nonliving?

Figure 8.2 shows Cairns-Smith AG discussing with Rautureau M. the enigma of "the origins of life" at Rautureau's home in Orléans, France. The photo was taken on March 16, 2010, when Cairns Smidth AG was on the road of Périgeux to his family property and spent 4 days in Orléans.

Cairns-Smith AG, an organic chemist and molecular biologist at the University of Glasgow, was famous by his controversial 1985 book entitled *Seven Clues to the Origin of Life* edited by Cambridge University Press. Much before of that date, Cairns Smidth AG had stayed few months at the University of Orléans trying to develop his knowledge on clay mineralogy. At that time Rautureau M and Caillère S, who was in-charge of the meteorite collection of the Paris Museum, were studying the origins of carbon in carbonaceous meteorites.

Caillère and Rautureau (1974) were within the first researchers to identify clay minerals in samples of three carbonaceous meteorites ("Alais," "Orgueil", and "Cold Bokkeveld") analyzed by electron microscopy and diffraction; *montmorillonite*, a hydrous phyllosilicate and clay mineral, was identified in samples of the meteorites referred to which had not been submitted to any kind of chemical treatment, indicating that its formation happened in a water-bearing environment. Carbonaceous chondrite meteorites contain no more than 2–3% of carbon by weight in organic matter, but they are important because of the insights they provide into the early history of the solar system, since they represent some of the most pristine matter known. Carbonaceous chondrites are primitive and undifferentiated

Fig. 8.2 Cairns-Smith AG (on the right) and Rautureau M (on the left) discussing the enigma of "the origins of life" at Rautureau's home in Orléans, France

meteorites whose parent bodies are Outer Main Belt asteroids. Certain families of carbonaceous chondrite meteorites as are the cases of CM (Mighei type) and CI (Ivuna type) are characterized by abundant hydrous phyllosilicates that may attain 90%, whose formation is the result of pervasive (Vebel and Palmer 2011), low-temperature (Tomeoka and Buseck 1985; McSween et al. 2003), and aqueous alteration post accretion of parent asteroids (McAdam et al. 2014).

In the aforesaid book, Cairns-Smith AG argues that organisms evolved from minerals, in particular from clay minerals, such as *kaolinite*.

In fact, we now know that clay minerals are unique nanosized minerals plenty of structural defects, some causing the overall negative electric charge responsible for their reactivity and catalytical activity, and on the Earth's surface or near surface, clay minerals are in continuous crystallochemical change and adaptation to environment changes, imitating natural selection and evolution.

Experimentally, Ferris (2005) has shown that the polymerization of RNA monomers in oligomers can be catalyzed by the clay mineral *montmorillonite*, and he argues that life would have begun with the first self-replicating genetic molecule, such as RNA, which formed the clay mineral that might have adsorbed, selected, organized, and catalyzed the building blocks of life's genetic machinery.

Meunier et al. (2010) state that *Fe-Mg smectites* would be formed from weathering and/or hydrothermal alteration of basalt-komatiite rocks predominant on the Earth's crust during the Hadean eon to early Archean eon (where life is assumed to have appeared), under the form of pillow lava and under reduced conditions, and would be altered by seawater. The high catalytic potentiality of this type of clay minerals, particularly the Fe^{2+}-rich ones, being potential electron exchangers, make them highly reactive. The authors suggest experiments regarding the synthetizing of prebiotic molecules using *Fe-rich clays* of *nontronite* type rather than *Al-montmorillonite*.

Hansma (2010) giving continuity to the previous investigations (Hansma, 2007, 2009) proposes the mica hypothesis that according to the author brings new ideas about the origins of life providing simple solutions to many basic questions. Muscovite mica is a hydrous phyllosilicate whose structure is based on a structural unit layer symbolized by T:O:T and can be classified as a specific clay mineral species. The mica interlayer compartment spaces, as a rule occupied by ions K^+, can function as the earliest "cells." Living cells have high internal K^+ concentration, and extracellular fluids are high in Na^+ concentration, a fact attributed to the mineral water (from the oceans or from hydrothermal springs) rich in Na^+ and poor in K^+, generally assumed as the natural environment where life has begun. The author describes the hypothetical "mica world" and the research carried out on the relationships between the mica world and the origin of life:

> In the – mica world – life would had evolved in large part from the organic molecules that were synthesized in "molecule mashers", pairs of mica layers that move up and down, towards each other and away from each other, mashing together and pulling apart whatever molecules are in the way, the necessary energy input to the molecules is mechanical from moving mica layers.

The author asks where K^+ did come from, and for himself life imitates mica in many ways, since it is organized into compartments that could be called cells, the mica sheets being held together by K^+ occupying individual compartments along mica interlayer spaces. Mica's thin flexible mineral sheets may have provided some of the protection to the primitive biomolecules that now is provided by the membrane lipid bilayers. In the mica hypothesis, multicellularity existed independently of lipids, in the multiple niches existing between mica layers, as in the RNA world. It is well known that besides muscovite mica there are other mica minerals rich in K^+, as is the case, for instance, of the so-called illite minerals, although of smaller crystal size, which are widespread at the Earth's surface. Mica unit layer has high electric charge comparatively to the other clay minerals, and at the interlayer spaces K^+ can be exchanged for Ca^{2+}, Mg^{2+}, H^+, and NH_4^+.

It can be said that life appeared with the transition of geochemistry to biogeochemistry, i.e., with the transition from a prebiotic Earth to the Earth man inhabits, and mineral evolution (Hazen 2005; Hazen et al. 2008). According to Hazen et al. (2013) clay minerals were absent prior to the planetesimal formation approximately 4.6 billion years ago but today are abundant in all near-surface Earth environments.

New clay mineral species (actually nearly 70 species are known) and modes of clay minerals paragenesis occurred as a consequence of major events in Earth's evolution. The changing character of clay minerals through time exemplifies the principles of mineral evolution. Clay minerals highlight the coevolution of Earth's geosphere and biosphere. Clays likely played critical roles in the origin of life, and life has played a dramatic role in the production of near-surface clay minerals.

In the USA, in 2006, the UC Riverside, in California, led a study reported in Science Express (Feb. 2 issue, https://newsroom.ucr.edu/1235) providing information pointing out that clay made animal life possible on Earth. Expansion of animal life on Earth, exemplified by the Cambrian explosion, has occurred just as the rate of clay formation on the Earth's surface also increased. The study led by Martin Kennedy indicates for the first time that the initial soils covering the terrestrial surface of Earth increased the production of clay minerals and provided the critical geochemical processes necessary to oxygenate the atmosphere and support multicellular animals. In late Precambrian, oxygen suddenly increased on Earth's atmosphere, and the increase in clay formation and oxygen shortly preceded – in geological time – the first animal fossils about 600 million years ago. Clay minerals form in soils through biological interactions with rocks weathering, and the soils are then eroded and flushed to the sea, where soil's finest particles are deposited as mud. Because clay minerals are chemically reactive, they attract and absorb organic matter in ocean water and physically shelter and preserve it. Organic matter preservation results in an equal portion of oxygen released to the atmosphere through the chemical reaction of photosynthesis. Thus, an increase in the burial of organic carbon made it possible for more oxygen to escape into the atmosphere.

The referred to relationship between clay formation expansion and animal life expansion requires to be scientifically confirmed. The clay hypothesis for the creation of life, within the analyzed hypotheses herein summarized, has significant experimental support, a reason why the basic information that shows the historical development of this hypothesis is herein disclosed.

In recent years the contribution of physics and chemistry for the emergence of life has been retaken by some groups of researchers who in their investigation attribute to some clay-type minerals, the anion-exchanging clays classified as hydrotalcites or layered double hydroxiodes (LDH) could have played decisive role since they can absorb "as guests" in their interior galleries the organic anions that could be fundamental for life's origin. Duval et al. 2019, 2020, argue that life is all about processes which would not happen spontaneously. On the contrary the processes are driven "uphill" by free energy – electrochemical disequilibria in the environment. The phenomenon life would involve the transformation of randomly dispersed chemical elements and molecules into highly ordered structures and reaction networks, proper of living beings, through electron transfer from reducing environmental compounds to oxidizing ones. To fulfill such purpose the authors provide very interesting arguments supporting the role of some minerals represented by the Green Rust minerals in life's emergence. Based on the specific structural, mechanodynamic and electrochemical properties of these minerals the authors propose a scenario for life's emergence mediated by Green Rust (GR) minerals in the framework of the alkaline hydrothermal vent hypothesis. Green Rust (GR) minerals have common occurrences, for instance the fougérite group minerals that is part of the hydrotalcites or layered double hydroxides (LDH) supergroup are characterized by being anion-exchanging clays able to harbour metal ions in their internal galleries similarly to the real clay minerals which can harbour in their interlayers metal ions which mimic the catalytic sites of bioessential metalloenzymes making them good candidates for the very earliest catalysts, rather more effective than the real cationic clays. Fougérite, $[(Fe^{2+}, Mg^{2+})_{1-x}\ Fe\ ^{3+}x\ (OH_2)x+(x/nA^{n-}.\ mH_2O)^{x-}]$, is the natural form of Green Rust. It was identified in waterlogged soils of gleyic properties under the forest in Fougères, Brittany, France, and exhibits green or bluish-green colour due to the existance of mixed valence Fe(II)-Fe(III) compounds (Duval et al., 2019; Génin et al., 2014). Fougerite´s mechanistic and catalytic specificities properties, the ability to absorb and incorporate in their structural galleries anions such as CO_3^{2-} and $PO_4^{3-\backslash}$, could have played important roles for life's emergence.

8.4 Hydrothermal Chimney or Vent Hypothesis

There are also researchers who admit that the earliest forms of life on Earth originated in hydrothermal chimneys or underwater hydrothermal vents, in which environments there are chemical-synthetic or chemical-autotrophic bacteria that form the basis of the food chain of complex communities of greater density and diversity near the chimneys than away from them; those bacteria convert heat, methane, and sulfur compounds into energy.

In 1977 the first deep-sea hydrothermal vent was discovered in the East Pacific Rise mid-oceanic ridge, using the submersible Alvin. The vent was characterized by "black smokers" and geothermally heated water up to 400 °C with high level of metal-bearing sulfides that precipitate in contact with the cold oceanic water. From that date on, other hydrothermal vents characterized by distinctive characteristics and flourishing life were identified in oceanic environments.

Submarine hydrothermal vents were first proposed as possible sites for the origin and early evolution of life by Corliss et al. (1981) and Baross and Hoffman (1985). Such hypothesis was further developed by Russell and Hall (1997), who proposed that the emergence of life within iron-sulfide bubbles of "black smokers" formed at the contact between hot alkaline hydrothermal fluids and cold acid seawater. Wachtershauser (1988) and Holm and Charlou (2001) also supported this same hypothesis. Hydrothermal fluids contain salts and organic molecules essential for both prebiotic chemistry and for primitive metabolisms (Holms and Charlou 2001).

In the hydrothermal chimneys or underwater hydrothermal vents, when the geothermally heated water that can reach temperatures up to 400 °C comes into contact with the cold sea water can lead to the precipitation of metals that eventually accumulate in the seabed producing chimney-like structures rich in polymetallic massive sulfides of high economic interest.

Metal sulfides have been proposed as key players in the prebiotic process in a scenario of "iron-sulfur world" (Wachtershauser 2007). This author considers that life began on the surface of iron-sulfur minerals and that a "pioneer organism" which contained a transition metal center to catalyze carbon fixing pathways to harness energy emerged from a high-pressure and high-temperature environment, like the one that prevails in the oceanic hydrothermal vents. This theory does not explain how this type of system would evolve.

According to Corliss et al. (1981), and Westall et al. (2018), hydrothermal vents are interesting prebiotic chemical systems for life's origin, but it is a scenario scientifically implausible without laboratory validation, since the dispersive environment of the oceans works against chemical concentration and cycling. Naturally the shallow-seated hydrothermal vents (e.g., up to 10 m depth, sunlight is another energy source) would be more favorable comparatively to the deep-seated hydrothermal vents, since sunlight would be another energy source. Decades of experiments in laboratory simulations of vent environments have failed to produce more than trace amounts of amino acids or of any other building blocks of biopolymers or membranes.

Against the hydrothermal vent hypothesis, it has been argued that the ionic strength and the ocean salinity and acidity (the result of the high levels of CO_2 existing in the early earth atmosphere) would severely limit the facilitation of the fundamental processes that are considered to be important for the formation of protocellular entities by self-assembly of amphiphiles and the nonenzymatic polymerization of mononucleotides.

8.5 Terrestrial Hot Spring Hypothesis

Several researchers are supporting the hypothesis that life has originated in terrestrial hot spring fields, environments rather more favorable than those at deep-sea hydrothermal vents, since they do not have the constraints referred to in hypothesis 3. The surface pools existing in such hot spring fields on land associated with volcanic activity (around geysers and hot springs) are favorable sites to concentrate in-fall from meteoritic sources and interplanetary dust particles that may contain key building blocks including fatty acids, nucleobases, and amino acids (Martins et al. 2008). For instance, in the Yellowstone National Park hot spring field that already has been rather well studied, repeated wet-dry cycling occurs at the margins of the pools, in some cases many times per day. Also, water ionic strengths are much lower than those found in oceans. These conditions would favor the occurrence and sustenance of prebiotically pertinent processes.

Unlike to what happens with hydrothermal vent environments in which it is impossible to determine the exact ionic composition of prebiotic oceans, in terrestrial hot spring environments, one could make a good analogous approach to the environments found on the extant Earth, possibilitating laboratory studies as those carried out by Joshi et al..

The recently published articles by Damer and Deamer (2015), Damer (2016), Djokic et al. (2017), van Kranendonk et al. (2017), and Pearce et al. based on laboratory and field testing are excellent background to support the terrestrial hot spring hypothesis. Bruce Damer and David Deamer, researchers of the University of California Santa Cruz, USA, and great enthusiasts of the hot spring hypothesis for life's origin, propose a scenario from the interplanetary synthesis and deliver inputs to a volcanic landscape based on seven stages: synthesis, accumulation, concentration, cycling, distribution, adaptation, and colonization.

Van Kranendonk et al. (2018) state the existence of significant new chemical, geological, and computational evidence increasingly supporting the hypothesis that life originated in hot spring hydrothermal fields *on land*, rather than at deep-sea hydrothermal vents. Surface pools, more precisely hot spring pools, would have been able to concentrate in-fall from meteoritic sources and interplanetary dust particles and contain the key building blocks for life including fatty acids, nucleobases, and amino acids. The seeds of life would come from extraterrestrial sources, but life on Earth would be a homegrown phenomenon. The authors provide a broad framework of observations, a conceptual new model for biogenesis in anoxic hydrothermal fields involving seven stages (synthesis of organic compounds in space; accumulation and concentration in hydrothermal field pools of the in-fall from meteoritic sources and interplanetary dust particles that contain the key building blocks for life including fatty acids, nucleobases and amino acids; cycling in pools where protocells undergo selection toward an origin of life; distribution of the earliest forms of life along an adaptation pathway into ever more extreme environments such as lacustrine, salty estuarine, and tidal marine settings; adaptation; and colonization), and implications for an *origin of life on land*.

8.6 Serpentinite Hypothesis

In the last decade, a new theory has emerged that attributes to *serpentinization* as the origin of life. Serpentinites are metamorphic rocks of low grade and dark green color, formed by the hydrothermal alteration of ultramafic or ultrabasic rocks, as is the case of the rock called peridotite which, when they occur on or near the surface of the crust, represent pieces of the mantle that have been displaced here. The serpentinites are so-called because they contain serpentines, minerals that are hydrated magnesium phyllosilicates (so are also clay minerals), such as *lizardite*, $Mg_3Si_2O_5(OH)_4$; *antigorite*, $Mg_3Si_2O_5(OH)_4$; and *chrysotile*, $Mg_3Si_2O_5(OH)_4$, belonging to the group of clay minerals. These minerals, although they have the same chemical composition, have different internal structures, the reason why they are said polymorphs.

When ultramafic rocks, rich in *olivine*, $(Mg,Fe)SiO_4$, and *pyroxene*, $(Mg,Ca)SiO_3$, minerals, are shifted to the next surface of the earth crust, they are exposed to the so-called serpentinization alteration that is promoted by circulating water or seawater:

$$\text{olivine} + \text{pyroxene} + H_2O \rightarrow \text{serpentine} + \text{brucite} + \text{magnetite} + H_2$$

According to McCollon and Seewald, the evolution of hydrogen (H_2) and methane (CH_4), which are based on experiments being carried out are believed to be used by many microorganisms to acquire metabolic energy in a chemical-synthetic way, microorganisms that could be "modern analogues" of the microbial communities existing on primitive Earth and possibly other planetary bodies of the Solar System, such as the planet Mars where ultramafic rocks have already been identified and which potentially can harbor life, a situation also admitted on Titan and Europa moons of planet Jupiter. Also, the authors mention the following:

> The process of serpentinization creates strongly reducing conditions and produces fluids that are highly enriched in molecular hydrogen, and some microorganisms could exploit these compounds to gain metabolic energy and to generate biomass leading to the development of biological communities based on chemical energy rather than photosynthesis.

The generation of H_2 during serpentinization is a consequence of the coupling of H_2O reduction to the oxidation of ferrous iron (Fe^{2+}) derived from olivine and pyroxene to ferric iron (Fe^{3+}) that precipitates in mineral products (e.g., magnetite, $FeFe_2O_4$), a process that can be summarized by the expression:

$$2(FeO) + H_2O \rightarrow (Fe_2O_3) + H_2$$

The presence of ultramafic rocks draws attention to the possibility that serpentinites may be at the origin and initial evolution of life. According to Schulte et al. (2006), if life on Earth really did get its start at a serpentinite-hosted hydrothermal vent or spring, it raises the distinct possibility that life may also have gotten started at other serpentinite environments beyond Earth.

In Portugal there is an occurrence where active serpentinization recently has been a matter of great interest for scientists, even for some from NASA (National Aeronautics and Space Administration), in the USA. Such occurrence is located near Cabeço de Vide, village belonging to the municipality of Fronteira, in the province of Alto Alentejo. Serpentinization of dunite, ultrabasic rock, is caused by the sulfurous hyposaline sodic and calcic water from an aquifer formed along a fault that separates marble and dunite rocks. This mineral water with pH = 11.5, a value that is the highest so far known worldwide, emerges at 19 °C, and there are archeological records of being utilized for healing purposes by Romans in the second century B.C. Actually, this unique water is used for the treatment of rheumatic, respiratory, and dermal health disorders in a thermal resort named Termas da Sulfúrea, which is a bathhouse built on top of the Roman bathhouse.

8.7 Concluding Remarks

When, where, and how did life on Earth originate are still unsolved scientific questions. In a very recent scientific article, Dalai et al. (2016) make an excellent synthesis of the two theories, terrestrial and extraterrestrial, for the origin of life. No matter where life did start, it had to arise from nonliving matter.

The terrestrial hypothesis considers that the earliest living cells emerged on our planet billion years ago, as a result of chemical evolution from nonliving matter, in a process called *abiogenesis*. The terrestrial hypothesis is currently supported by knowledge of the flourishing life spanning unicellular and multicellular organisms that occurs in the so-called hydrothermal chimneys that emit black fluids and have been identified in certain places on the ocean floor characterized by extreme environments where temperatures between 250 and 400 °C, reduced species of transition metals as part of sulfides particularly minerals of the group of iron sulfides, very acidic pH (2–3), and high concentrations of gases (CO_2 and H_2S) do occur. This is what happens in the hydrothermal chimneys of the hydrothermal field Rainbow, in the Azores.

There is another type of oceanic hydrothermal chimneys that emit fluids of white color. These are the cases of the Lost City and Strytan fields that occur in the mid-Atlantic mountain range and northern Iceland, respectively. In them the temperature of the fluids regulates between 60 and 90 °C, the pH is alkaline (9–11), and the precipitation and the formation of deposits of calcium and magnesium carbonates of white color takes place. Both black fluids and white fluids can provide ideal environments for the emergence of primitive metabolisms (methanogenesis, acetogenesis, and methanotrophy) dispensing with the need for the world of preceding RNA.

Kawamura et al. detected amino acid oligomers in experiments simulating the conditions prevailing in black fluid-emitting hydrothermal systems. Also experiments carried out by McCollum in which the conditions prevailing in the hydrothermal systems were simulated identified the production of aliphatic and aromatic hydrocarbons and also carboxylic acids. Several other experiments have been carried out.

The *extraterrestrial hypothesis* admits that the source of organic prebiotics is related to impacts of meteorites and comets on the Earth's surface. Among the most primitive meteorites, the so-called carbonaceous chondrites contain about 2% carbon. More than 14,000 organic compounds, including 70 amino acids, which are considered the building blocks of life, have been identified (Dalai et al. 2016).

In meteorites the organic compounds can survive because only the outer layers of the meteorite are affected by the frictional heat generated in the penetration of the Earth's atmosphere. In fact, meteorite minerals or more precisely meteorite mineral analogs (the concept of mineral implies origin on Earth) are the vehicles that transport and protect from heat (thermal sterilization) and high-energy solar UV radiation the building blocks of life during the long journey through the interplanetary space to Earth. New research indicates that microorganisms could have survived a journey from Mars to Earth (Warmflash and Weiss 2005).

A decisive argument in favor of the *extraterrestrial* or *panspermia hypothesis* would be the discovering of life in other planets or in moons.

In all the five aforesaid hypotheses for the origin of life, two geologic resources play fundamental roles: *minerals* (including clay minerals, serpentine, mica, iron-sulfur minerals, metals, and mineral analogues with extraterrestrial origin which have been ridden to Earth on meteorites) and *mineral water* (from environments such as ocean, seaside pools, oceanic hydrothermal vents, and terrestrial hot springs).

Minerals, as chemical systems, provide the chemical elements entering in the formation of the life essential block units, and their reactive surfaces serve as support to the catalytic reactions needed to the self-organization and polymerization of the primitive biomolecules, the organic monomers (Lambert 2008; Cleaves et al. 2012).

Liquid water is generally considered as a prerequisite for the emergence of life on Earth, being most probably active in prebiotic chemistry as a clay mineral producer by weathering of primary rock-forming minerals. Also, water is a powerful hydrolytic chemical agent. Water, mineral salts (Na, K, Ca, Fe, Cl, S, and P), macromolecules (polymers made of C, O, H) such as DNA and RNA (polymers of nucleotide bases), proteins (polymers of amino acids), lipids (polymers of fatty acids), and carbohydrates (polymers of monosaccharides) are the fundamental components of cells.

There is a consensus that the interaction of organic molecules and the surfaces of naturally occurring minerals might have played a crucial role in chemical evolution and complexification in a prebiotic area. Rimola et al. present an interesting review, including personal experiments mainly focusing on prebiotic processes occurring on the mineral surfaces of four classes of minerals: clay minerals, titanium dioxide, iron sulfides, and silica and silicates. The authors identified the driving forces for the adsorption of the organic compounds, which depend on the mineral:

1. H bond interactions between H donor groups of the adsorbate and O (or S) atoms of the surfaces.
2. Covalent bonds.
3. Dispersive interactions between aliphatic/aromatic groups and nonpolar regions of mineral surfaces.
4. Electrostatic interactions, in the case of metal-containing clay minerals, in which isomorphic substitution is common.

Rimola et al. ended their review putting forward the following question:

> Could minerals if covered by short prebiotic building blocks exhibit "enzymatic" functionalities that activated and triggered fundamental catalytic cycles relevant for autotrophic chemical evolution and complexification?

Prebiotic organic synthesis catalyzed by natural metal sulfides is a key process for understanding the evolution of biochemistry from inorganic molecules (Li et al. 2018). For iron-sulfur minerals, essentially FeS_2 in which Fe is in its oxidized state, much work has been carried out, particularly on the interaction of glycine and its polymerization into peptides. Possible redox effects inferred by Fe^{2+}, for instance, in olivines, should be investigated. Metal sulfides have been proposed as key players in the prebiotic processes in several scenarios: "iron-sulfur world" (Wächtershäuser 1988, 2007), iron-sulfur membrane model (Russell and Hall 1997, 2006), the "Zinc world" (Lane and Martin 2012), and the "geoelectrochemistry-driven origin of life" (Nakamura et al. 2010; Yamamoto et al. 2018; Barge et al. 2015).

The origin and the evolution of life on Earth still remains a big enigma despite the rapid scientific advances in the fields of astrobiology, astrophysics, molecular biology, and genetics. Another big enigma is the origin of the universe; more than 95% of it is still unknown according to the Italian physicist Guido Tonelli, scientist of the European Organization for Nuclear Research (CERN) and one of the protagonists of the team that announced, on July 4, 2012, the discover of the subatomic elementary particle called Higgs boson in the Standard Model of particle physics, such particle being predicted by Peter Higgs in the 1960s. Tonelli (2020) produced a book entitled *Genesis: The Story of How Everything Began*, a short and humanistic tour of the origins of the Universe, Earth, and life – drawing on the latest discoveries in physics to explain the seven most significant moments in the creation of the cosmos. The author considers the incredible challenges scientists face in exploring the universe's mysteries.

Brack (2007) also produced an excellent article entitled "From the Origin of Life on Earth to Life in the Universe," which:

> Covers and discuss the different theories about the origin and evolution of life on Earth, and conclusions are drawn on the likelihood of life originating and persisting on other places of our solar system, such as the terrestrial planets and the moons of the giant planets, or beyond in the Universe.

The chapter on the search for life in the solar system really is very interesting, since it reports the experiments being carried out and the corresponding achievements.

A brief note to report is that on July 30, 2020, NASA (National Aeronautics and Space Administration), the US government organization, successfully launched its latest Mars rover, *Perseverance*, from Cape Canaveral, Florida, sending the space program's most sophisticated rover yet to the Red Planet that carries a suite of instruments to analyze rocks for "biosignatures" and collect rock samples that will enable scientists to potentially seek out signs of "ancient microbial life." The rover will be put on the most promising spot, the Jezero crater to the north of the planet's equator, where about 3500 million years ago would have been a lake and a river delta (on Earth all forms of life need water and energy), hoping that the sampled sediments keep signs of microbial life in the planet. This NASA mission was shortly preceded by two other missions. On July 19, 2020, from the Tanegashima Space Center, in Japan, the probe *Hope* was launched to study Mars' atmosphere, and on July 23, 2020, from the Wenchang Space Center, in Hainan island, in China, the probe *Tianwen-1* was launched transporting equipment to study Mars' climate and magnetic environment (clues to the planet's interior).

Expectations are high but unfortunately will be much delayed. The analytical results of the collected rock samples would not be known before the end of present decade.

On September 14, 2020, the journal *Nature Astronomy* reported the detection of *phosphine* or hydrogen phosphide, H_3P, in the upper atmosphere of the planet Venus where temperatures around 30 °C and pressures are similar to those prevailing on Earth. For the moment such finding could be a signal for the existence of life there, since that molecule in Earth is a marker of microbial life. On Earth *phosphine* is a gas produced by microbes which are developed in anerobic environments. In quite different environments, *phosphine* already had been identified in Jupiter's and Saturn's atmospheres.

Also, on October 20, 2020, NASA announced that the OSIRIS-REx spacecraft which for about 2 years was orbiting the assumed carbon-rich rocky Bennu asteroid located at about 321 million km away from the Earth has successfully descended on the asteroid surface to collect a sample of rock debris or regolith. The spheriform asteroid has a diameter estimated at around 500 meters, and the name OSIRIS-REx stands for origins, spectral interpretation, resource identification, security, and regolith explorer. OSIRIS-REx spacecraft is scheduled to return to Earth on September 24, 2023.

On December 6, 2020, Japan's Hayabusa2 spacecraft will return to Earth bearing a sample of surface debris of the asteroid Ryugu.

From the foregoing said, it is clear that research still goes on seeking the origins and evolution of life on Earth, on some other planets, and on some asteroids, and expectations are high regarding the understanding of the origin of both the solar system and life on Earth. Relevant information could be provided by the studies to be carried out on surface materials already sampled or hoping to be sampled on surface materials of Mars and of asteroids such as Ryugu, Bennu, and 16Psyche (this having a core assumed to be composed of metals such as Fe, Ni, and Au) utilizing spacecrafts used in space missions planned and already performed or on the way.

Besides the bibliographic references cited in the chapter's body, others are cited in the references list since they have provided interesting information regarding the preparation of the chapter, such as: Brazelton et al. (2012), Callahan (2011), Cairns-Smith (2008), Deamer & Georgiou (2015), de Duve (2003), dos Santos et al. (2016), Ehlmann et al. (2010), Ertem and Ferris (1996), Ferris (1992, 2006), Ferris and Ertem (1993), Ferris et al. (1996), Flores. et al (2011), Galvez-Martinez and Mateo-Marti (2018), Hashizume (2012), Hazen and Sverjensky (2010), Kee and Monnard (2016), Martins and Seewald (2013), Martins et al. (2007), Maurel & Leclerc (2016), McCollom and Seewald (2007), McCollom and Seewald (2013), McSween Jr et al. (2003), Ménez et al. (2012), Miller (1955), Miller and Lazcano (1995), Petersen et al. (2011), Rao et al. (1980), Sahai et al. (2016), Schrenk et al. (2013), Shapiro (1984), and Shapiro (2000).

References

Bada JL (2004) How life began on Earth: a status report. Earth Planet Sci Lett 226:1–15

Bada JL, Lazcano A (2002) Some like it hot, but not the first biomolecules. Science 296:1982–1983

Barge LM, Abedian Y, Russell MJ, Doloboff IJ, Cartwright JH, Kidd RD, Kanik K (2015) From chemical gardens to fuell cells: generation of electrical potential and current across self-assembling iron mineral membranes. Angew Chem 127:8302–8305

Baross JA, Hoffman SE (1985) Submarine hydrothermal vents and associated gradient environments as sites for the origin and evolution of life. Orig Life Evol Biosph 15:327–345

Bernal JD (1949) The physical basis of life. Proc Phys Soc Sect A 62:746–747

Brack A (2006) Chapter 7.4: Clay minerals and the origin of life. In: Developments in clay science, vol 1. Elsevier, pp 379–391

Brack A (2007) From the origin of life on earth to life in the universe. In: Horneck G, Rettberg P (eds) Complete course in astrobiology. WILEY-VCH Verlag GmbH & Co, Weinheim. ISBN: 978-3-527-40660-9

Brazelton WJ, Nelson B, Schrenk MO (2012) Metagenomic evidence for H oxidation and H production by serpentinite-hosted subsurface microbial communities. Front Microbiol 2. https://doi.org/10.3389/fmicb.2011.00268

Caillère S, Rautureau M (1974) Détermination des silicates phylliteux des météorites carbonées par microscopie et diffraction électroniques. C. R. Acad Sc. Paris, t 279 (12 août 1974), Série D -539

Cairns-Smith AG (1982) Genetic takeover. Cambridge University Press, Cambridge, 133pp

Cairns-Smith AG (1985) Seven clues to the origin of Life: a scientific detective story. Cambridge University Press, Cambridge. 131pp

Cairns-Smith AG (2002) The origin of life: clays. In: Frontiers of life, vol 1. Cambridge University Press, Cambridge, pp 169–192

Cairns-Smith AG (2005) Sketches for a mineral genetic material. Elements 1:157–161

Cairns-Smith AG (2008) Chemistry and the missing era of evolution. Chem Eur J 14:3830–3839

Cairns-Smith AG, Hartman H (1986) Clay minerals and the origin of life. Cambridge University Press, Cambridge, 193pp

Callahan MP et al (seven co-authors) (2011) Carbonaceous meteorites contain a wide range of extraterrestrial nucleobases. PNAS (Proccedings of the National Academy of Sciences) of the United States of America 108, 13995–13998

Callahan MP, Smith KE, Cleaves HJ, Ruzicka J, Stern JC, Glavin DP, House CH, Dworkin JP (2011) Carbonaceous meteorites contain a wide range of extraterrestrial nucleobases. PNAS, Organic Chemistry, Thiemens MH (editor)

Cleaves HJ, Scott AM, Hill FC, Leszczynski J, Sahai N, Hazen R (2012) Mineral-organic interfacial processes: potential roles in the origins of life. Chem Soc Rev 41:5502–5525

Corliss JB, Baross JA, Hoffman SE (1981) A hypothesis concerning the relationship between submarine hot springs and the origin of life on Earth. Oceanol Acta 4(suppl):59–69

Dalai P, Kaddour H, Sahai N (2016) Incubating life: prebiotic sources of organics for the origin of life. Elements 12(6):401–406

Damer BF (2016) A field trip to the Archaean in search of Darwin's warm little pond. Life 6(2):21

Damer BF, Deamer DW (2015) Coupled phases and combinatory selection in fluctuating hydrothermal pools: a scenario to guide experimental approaches to the origin of cellular life. Life 5:872–887

de Duve C (2003) A research proposal on the origin of life. Orig Life Evol Biosph 33:559–574

Deamer DW, Georgiou CD (2015) Hydrothermal conditions and the origin of cellular life. Astrobiology 15:1091–1095

Djokic T, van Kranendonk MJ, Campbell KA, Walter MR, Ward CR (2017) Earliaest signs of life on land preserved in ca. 3.5Ga hot spring deposits. Nat Commun:15263

dos Santos R, Patel M, Cuadros J, Martins Z (2016) Influence of mineralogy on the preservation of amino acids under simulated Mars conditions. Icarus 277:342–353

Duval S, Baymann F, Schoepp-Cothenet B, Trolard F, Bourrié G, Grauby O, Branscomb E, Russell M, Nitschke W (2019) Fougerite: The not so simple progenitor of the first cells. Interface Focus 9: 20190063, The Royal Society Publishing

Duval S, Branscomb E, Trolard F, Bourrié G, Grauby O, Heresanu V, Schoepp-Cothenet B, Zuchan K, Russell M, Nitsche W (2020) On the why's and how's of clay minerals importance in life's emergence. Appl Clay Sci 195:105737. https://doi.org/10.1016/j.clay.2020.105737

Ehlmann BL, Mustard JF, Murchie SL (2010) Geologic setting of serpentine deposits on Mars. Geophys Res Lett 37. https://doi.org/10.1029/2010GL042596

Ertem G (2004) Montmorillonite, Oligonucleotides, RNA and Origin of Life. Orig Life Evol Biosphere 34:549–570

Ertem G, Ferris JP (1996) Synthesis of RNA oligomers on heterogeneous templates. Nature 379:238–240

Ferris JP (1992) Marine hydrothermal systems and the origin of life: chemical markers of prebiotic chemistry in hydrothermal systems. Orig Life Evol Biosphere 22:109–134. https://doi.org/10.1007/BF01808020

Ferris JP (2005) Mineral catalysis and prebiotic synthesis: montmorillonite-catalyzed formation of RNA. Elements 1:145–149

Ferris JP (2006) Montmorillonite-catalysed formation of RNA oligomers: the possible role of catalysis in the origins of life. Phil Trans Royal Soc B 361:1777–1786

Ferris JP, Ertem G (1993) Montmorillonite catalysis of RNA oligomer formation in aqueous solution: a model for the prebiotic formation of RNA. J Am Chem Soc 115, 12270–12275

Ferris JP, Hill AR Jr, Liu R, Orgel LE (1996) Synthesis of long prebiotic oligomers on mineral surfaces. Nature 381:59–61

Flores GE and 10 co-authors (2011) Microbiam community structure of hydrothermal deposits from geochemically different vent fields along the Mid-Atlantic Ridge. Environ Microbiol 13, 2158–2171

Galvez-Martinez S, Mateo-Marti E (2018) Utraviolet irradiation on a pyrite surface improves triglycine adsorption. Life 8:50. https://doi.org/10.3390/life8040050

Gilbert W (1986) Origins of life: the RNA world. Nature 318:618

Goldschmidt VM (1952) Geochemical aspects of the origin of complex organic molecules on the Earth, as precursors to organic life. New Biol 12:97–105

Guttenberg N, Virgo N, Chandru K, Scharf C, Mamajanov I (2017) Bulk measurements of messy chemistries are needed for a theory of the origins of life. Philos Trans A Math Phys Eng Sci 375:20160347

Hansma HG (2007) Mica and the origin of life: Cells without membrane. Mol Biol Cell 18 (suppl.), Abstract: 1910

Hansma HG (2009) Could life originate between mica sheets? Mechanochemical biomolecular synthesis and the origins of life. In: Tamura N (ed) Probing mechanics at nanoscale dimensions, vol 1185. Materials Research Society, Warrendale, pp 1103–1115

Hansma HG (2010) Possible origin of life between mica sheets. J Theor Biol 266:175–188

Hashizume H (2012) Chapter 10: Role of clay minerals in chemical evolution and the Origins of Life. In: Clay minerals in nature – their characterization, modification and application. InTECH, pp 191–208

Hazen RM (2005) Genesis: rocks, minerals and the geochemical origin of life. Elements, an International Magazine of Mineralogy, Geochemistry and Petrology 1:135–137

Hazen RM, Sverjensky DA (2010) Mineral surfaces, geochemical complexities, and the origins of life. Cold Spring Harb Perspect Biol 2

Hazen RM, Papineau D, Bleeker W, Downs RT, Ferry JM, McCoy TJ, Sverjensky DA, Yang H (2008) Mineral evolution. Am Mineral 93:1693–1720

Hazen RM, Sverjensky DA, Azzolini D, Bish DL, Elmore AC, Hinnov L, Milliken RE (2013) Clay mineral evolution. Am Mineral. https://doi.org/10.2138/am.2013.4425

Holm NG (1992) Why are hydrothermal systems proposed as plausible environments for the origin of Life? Orig Life Evol Biosph 22:5–14

Holm NG, Charlou JL (2001) Initial indications of abiotic formation of hydrocarbons in the Rainbow ultramafic hydrothermal system, Mid-Atlantic Ridge. Earth Planet Sci Lett 191:1–8

Hoyle F, Wickramsinghe NC (1977) Polysaccharides and the infrared spectra of galactic sources. Nature 268:6109

Hoyle F, Wickramsinghe NC (2000) Astronomical origin of life, steps towards panspermia. Kluwer Academic Press, Dordrecht

Kee TP, Monnard P-A (2016) On the emergence of a proto-metabolism and the assembly of early protocells. Elements 12(6):419–424

Kitadi N, Maruyama S (2018) Origins of building blocks of life: a review. Geosci Front 9:1117–1153

Kvenvolden KA, Lawless JG, Pering K, Peterson E, Flores J, Ponnamperuma C, Kaplan JR, Moore C (1970) Evidence for Extraterrestrial amino acids and hydrocarbons in the Murchinson ALH84001 meteorite. Nature 228:923–926

Lambert J-F (2008) Adsorption and polymerization of amino acids on mineral surfaces: a review. Orig Life Evol Biosph 38:211–242

Lambert J-F (2015) Origins of Life: From the mineral to the biochemical world. BIO Web of Conferences 4, 00012, https://doi.org/10.1051/bioconf/20150400012, EDP sciences

Lane N, Martin WF (2012) The origin of membrane bioenergetics. Cell 151:1406–1416

Lanier KA, Williams LD (2017) The origin of life: models and data. J Mol Evol 84:85–92. https://doi.org/10.1007/s00239-017-9783-y

Lazcano A, Miller SL (1994) How long did it take for life to begin and evolve to cyanobacteria? J Mol Evol 39:546–554

Li Y, Kitadi N, Nakamura R (2018) Chemical diversity of metal sulfide minerals and its implications for the origin of life. Life 8(46). https://doi.org/10.3390/life8040046

Liu T, Temprano I, Jenkins SJ, King DA, Driver SM (2012) Nitrogen adsorption and desorption at iron pyrite FeS2 100 surfaces. Phys Chem Chem Phys 14:11491–11499

Liu T, Temprano I, Jenkins SJ, King DA, Driver SM (2013) Low Temperature Synthesis of NH3 from Atomic N and H at the surfaces of FeS2{100} Crystals. J Phys Chem 117:10990–10998

Llorca J (2004) Organic matter in meteorites. Int Microbiol 7:239–248

Martin W, Russell MJ (2002) On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. Philos Trans R Soc Lond B 385:59–85

Martin W, Russell MJ (2007) On the origin of biochemistry at an alkaline hydrothermal vent. Philos Trans R Soc Lond B Boil Sci 362:1887–1925

Martin W, Baross J, Kelley D, Russell MJ (2008) Hydrothermal vents and the origin of life. Nat Rev Microbiol 6:805–814

Martins Z (2011) Organic chemistry of carbonaceous meteorites. Elements 7(1):35–40

Martins Z, Seewald JS (2013) Serpentinites, hydrogen and life. Elements 9:129–134

Martins Z, Alexander CMO, Orzechowska GE, Fogel M, Ehrenfreund P (2007) Indigenous amino acids in primitive CR meteorites. Meteorit Planet Sci 42(2):2125–2136

Maurel MC, Leclerc F (2016) From foundation stones to life: concepts and results. Elements 12(6):407–412

McAdam MM, Sunshine JM, Howard KT, McCoy TM (2014) Spectral trends in aqueously altered CM/CI meteorites. In the Abstracts Book of the 51st Annual Meeting of CMS, "Everything is Big: From Nanoparticles to Planets", pp 166–167

McCollom TM, Seewald JS (2007) Abiotic synthesis of organic compounds in deep-sea hydrothermal environments. Chem Rev 107:382–401

McCollom TM, Seewald JS (2013) Serpentinites, hydrogen and life. Elements 9:129–134

McKay DS, Gibson EK, Thomas-Kerpta KL, Vali H, Romanek CS, Clemett SJ, Chillier DF (1996) Search for past life on Mar: Possible relic biogenic activity in Martian meteorite ALH84001. Science 273(issue 5277):924–930

McSween HY Jr, Ghosh A, Grimm RE, Wilson L, Young ED (2003) Thermal evolution models of asteroids. In: Bottke WF Jr et al (eds) Asteroids III. Univ. of Arizona, Tucson, pp 559–571

Ménez B, Pasini V, Brunelli D (2012) Life in the hydrated suboceanic mantle. Nat Geosci 5:133–137

Meunier A, Petit S, Cockell CS, El Albani A, Beaufort D (2010) The Fe-rich clay Microsystems in basalt-komatite lavas: importance of Fe-smectites for pre-biotic molecule catalysis during the Hadean eon. Orig Life Evol Biosph, Springer. https://doi.org/10.1007/s11084-010-9205-2

Miller SL (1953) A production of amino acids under possible primitive Earth' conditions. Science 117:528–529

Miller SL (1955) Production of some organic compounds under possible primitive Earth' conditions. J Am Chem Soc 77:2351–2361

Miller SL, Lazcano A (1995) The Origin of Life: did it occur at high temperatures? J Mol Evol 41:689–692

Miller SL, Orgel LE (1974) The origins of life on the earth. Englewood Cliffs (NJ), Prentice Hall

Miller SL, Urey HC (1959) Organic compound synthesis on the primitive Earth. Science 130:245–251

Morrison SH, Runyon SE, Hazen RM (2018) The paleomineralogy of the Hadean Eon Revisited. Life 8:64. https://doi.org/10.3390/life8040064

Nakamura R, Takashima T, Kato S, Takai K, Yamamoto M, Hashimoto K (2010) Electrical current generation across a black smoker chimney. Angew Chem 122:7858–7860

Oparin AI (1938) The Origin of the Life. MacMillan, New York. (Original in Russian, 1924)

Orgel LE (1986) RNA catalysis and the origin of life. J Theor Biol 123:127–149

Petersen JM et al (2011) Hydrogen is an anergy source for hydrothermal vent symbioses. Nature 476:176–180

Pross A (2004) Causation and the origin of life: metabolism or replication first? Orig Life Evol Biosph 34:307–321

Rao M, Odom DG, Oró J (1980) Clays in prebiological chemistry. J Mol Evol 15(4):317–331

Russell MJ (2003) The importance of being alkaline. Science 302:580–581

Russell MJ, Hall AJ (1997) The emergence of life from iron monosulphide bubbles at a submarine hydrothermal redox and pH front. J Geol Soc Lond 154:377–402

Russell MJ, Hall AJ (2006) The onset and early evolution of life. In: Memoir 198: evolution of early's earth atmosphere, hydrosphere, and biosphere constraints from ore deposits. Geological Society of America, Boulder, pp 1–32

Russell MJ, Hall AJ, Mellersh AR (2003) On the dissipation of thermal and chemical energies on the Early Earth. In: Natural and laboratory-simulated thermal geochemical processes. Springer, Dordrecht, pp 325–388

Sahai N, Kaddour H, Dalai P (2016) The transition from geochemistry to biogeochemistry. Elements 12(6):389–394

Saladino R, Neri V, Crestini C, Costanzo G, Graciotti M, Di Mauro E (2008) Synthesis and degradation of nucleic acid components by formamide and iron sulfur minerals. J Am Chem Soc 130:15512–15518

Schoonen M, Smirnov A (2016) Staging life in an early warm 'seltzer' ocean. Elements 12:395–400

Schopf JW (1993) Microfossils of the Early Archean Apex Chert: new evidence of the antiquity of life. Science 260:640–646

Schrenk MO, Brazelton WJ, Lang SQ (2013) Serpentinization, carbon, and deep life. Rev Mineral Geochem 75:575–606

Schulte M, Blake D, Hoehler T, McCollom TM (2006) Serpentinization and its implications for life on the early Earth and Mars. Astrobiology 6:364–376

Shapiro R (1984) The improbability of prebiotic nucleic acid synthesis. Orig Life 14:565–570

Shapiro R (2000) Hypothesis paper: A replicator was not involved in the origin of Life. IUBMB Life 49:173–176

Shapiro R (2006) Small molecule interactions were central to the origin of Life. Q Rev Biol 81(2):105–125

Southam G (2012) Minerals as Substrates for Life: The Prokaryotic View. Elements 8:101–106

Tawfik DS (2010) Messy biology and the origins of evolutionary innovations. Nat Chem Biol 6:692–696

Tomeoka K, Buseck PR (1985) Indicators of aqueous alteration in CM carbonaceous chondrites: Microtextures of a layered mineral containing Fe, S, O, and Ni. Geo Cosmo Acta 49(10):2149–2163. https://doi.org/10.1016/0016-7037(85)90073-0

Tonelli G (2020) Genesis: the story of how everything eegan. Farrar, Straus, Giroux (publishers), 224pp, ISBN: 9780374600488

Urey HC (1952) On the early chemical history of the Earth and the origin of Life. Proc Natr Acad Sci USA 38:351–363

Van Kranendonk M, Deamer D, Djokic T (2017) Life springs: life on Earth came from a hot volcanic pool, not the sea, new evidence suggests. Sci Am 317(2):28–35

Van Kranendonk M, Baumgartner R, Boyd E, Cady S, Campbell K, Czaja A, Damer B, Deamer D, Djokic T, Fiorentini M, Gangidine A, Havig J, Mulkidjanian A, Ruff S, Thordarson P (2018) Terrestrial hot springs and the origin of Life: implications for the search for life beyond earth. 49th Lunar and Planetary Ecience Conference 2018 (LPI Contrib. n. 2083)

Velbel MA, Palmer EE (2011) Fine-grained serpentine in CM2 carbonaceous chondrites and its implications for the extent of aqueous alteration on the parent body: a review. Clay Clay Miner 59:416–432

Wade N (2003) How did life begin? The New York Times 11 November: F11

Warmflash D, Weiss B (2005) Did life come from another world? Sci Am 293(5):64–71

Westall F, Hickman-Lewis K, Hinmam N, Gautret P, Campbell KA, Bréhéret JG, Foucher F, Hubert A, Sorieul S, Dass AV, Kee TP, Georgelin T, Brack A (2018) A hydrothermal-sedimentary context for the origin of life. Astrobiology 18(3):259–293. https://doi.org/10.1089/ast.2017.1680

Wächtershäuser G (1988) Before enzymes and templates: theory of surface metabolism. Microbiol Rev 52:452–484

Wächtershäuser G (1992) Groundworks for an evolutionary biochemistry: the iron-sulphur world. Prog Biophys Mol Biol 58:81–201

Wächtershäuser G (2007) On the chemistry and evolution of the pioneer organism. Chem Biodivers 4:584–602

Yabuta H, Sandford SA, Meech KJ (2018) Organic molecules and volatiles in comets. Elements 14(2):101–106

Yamamoto M, Hakamura R, Takai K (2018) Deep-sea hydrothermal fields as natural power plants. ChemElectroChem 5:2162–2166

Zahnle KJ (2006) Earth's earliest atmosphere. Elements 2:217–222

Zubay G (2000) Origins of life on the earth and in the cosmos, 2nd edn. Academic Press, San Diego

Chapter 9
Minerals in Pharmacy and Cosmetics

Celso S. F. Gomes, Delfim F. G. Santos, and Maria Helena R. Amaral

Abstract Since remote times, some minerals have been used in medicines and cosmetics, alone or in mixtures. The advantage of minerals in pharmaceuticals and cosmetics is the fact that they are natural and that in adequate proportions they are harmless. On the one hand, some minerals are used as active substances or ingredients in pharmaceuticals; examples and their specific roles are reported and discussed. Also, some minerals are used as excipients in pharmaceutical preparations to enhance their organoleptic characteristics, to improve their physicochemical properties, and to facilitate the elaboration, conservation, and liberation of the active ingredient inside the organism. On the other hand, some minerals are used in cosmetics as active ingredients and excipients. At last the chapter provides information about the guidelines relative to elements and minerals that as impurities could be present in pharmaceuticals and cosmetics, as well as about cosmetic microbiology and antimicrobial protection.

9.1 Background Data

Since remote times, minerals have been used in medicines and cosmetics, alone or in mixtures. Currently, many medicinal or cosmetic products are based on minerals such as *montmorillonite*, *kaolinite*, *sulfur*, *halite*, *sylvite*, *calcite*, *kieserite*, *talc*, and many others.

Mesopotamians are considered to be the first to introduce minerals in cosmetics using mineral pigments, green, blue, red, yellow, brown, black, and white. Green and blue pigments could be derived from copper-bearing minerals; red, yellow, and brown pigments could derive from iron oxides and hydroxides; black pigments

---

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit “GeoBioTec”,
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

D. F. G. Santos · M. H. R. Amaral
Faculty of Pharmacy, University of Porto, Porto, Portugal
e-mail: dsantos@ff.up.pt; hamaral@ff.up.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_9

would have been derived from manganese oxides and hydroxides; and the white pigments could be derived from calcium carbonates, lead carbonate (*cerussite*), and *bioapatite* (derived from animal bone). Butler (2000) in an article entitled "Cosmetics through the Ages" discloses information about the historical evolution of cosmetics.

Selected minerals provide to mineral-based products various properties that can be beneficial for the body; e.g., they can act as disinfectant or as astringent, provide nutritional microelements, etc. Minerals are successfully used not only in pharmacy, but also in therapeutic mud/peloid baths, brine baths, mud/peloid treatments, and others.

The two last decades of the twentieth century were characterized by the first real investigations on the role of minerals in pharmacy, cosmetics, and medicine (Browne et al. 1980; Hermosin et al. 1981; White and Hem 1983; Messina and Grossi 1983; Galán et al. 1985; Savarit 1987; Sanchez-Martin et al. 1988; Torresani 1990; Ferrand and Yvon 1991; Oya et al. 1992; Ueda and Hamayoshi 1992; Gamiz et al. 1992; Venialle 1992; Bettero et al. 1994a, b; Braun 1994; Madkour et al. 1993; Robertson 1996; Veniale 1996; De Bernardi and Pedrinazi 1996; Novelli 1996; López-Galindo and Viseras 1996; Yvon and Ferrand 1996; Cara et al. 1996; Bertolani and Loschi-Ghittoni 1996). For instance, the advantage of minerals in cosmetics is because they are natural, and if in adequate proportions, they are harmless. Cosmetics containing geothermal mineral water, if properly applied, have a beneficial effect on the skin, but also through percutaneous absorption, on the whole body, due to the significant content of elements necessary for proper functioning of organs and tissues. The applied cosmetics are easily washed off with water, and their effect occurs mainly at the time when they are on the skin. Due to percutaneous absorption, the chemical elements absorbed from minerals are transported through the circulatory system and distributed throughout the body.

Cosmetics are used to change the human body characteristics in order to improve beauty and wellness. Natural and synthetic ingredients participate in cosmetic formulation. The efficacy of cosmetic products is tested both in animals and in vitro. The safety of cosmetic and drug products is worldwide assured by regulatory agencies, such as the Food and Drug Administration (FDA) in the USA and The Scientific Committee on Consumer Safety (SCCS), in Europe.

With a wide range of physical, chemical, and physicochemical properties, clay minerals have an undisputable role in pharmaceutical industries.

In terms of general chemical composition, the minerals employed primarily in pharmacy and cosmetics are classified as oxides, carbonates, sulfates, chlorides, hydroxides, sulfides, phosphates, nitrates, borates, and phyllosilicates.

Within phyllosilicates the clay minerals are widely used due to their unique properties with unique contributions both in therapeutics and cosmetics. Clay minerals being biologically compatible can ensure the creation of safe and effective drug delivery systems. The desirable physical and physicochemical properties of clay minerals have led them to play a substantial role in pharmaceutical formulations.

Clay minerals such as *kaolinite*, *halloysite*, *talc, montmorillonite*, *palygorskite*, *and sepiolite* are among the world's most valuable industrial minerals and of considerable importance in pharmacy and cosmetics (Carretero 2002; López-Galindo and Viseras 2004; Carretero et al. 2006; Carretero and Pozo 2007; Carretero et al. 2007; Viseras et al. 2007; López-Galindo et al. 2011).

The elemental features or characteristics of clay minerals which justify their uses in pharmaceutical formulations are as follows: high specific area, sorption capacity, favorable rheological properties, chemical inertness, swelling capacity, reactivity to acids, and inconsiderable toxicity.

Clay minerals are used as excipients in pharmaceutical preparations to enhance their organoleptic characteristics, such as flavor (flavor correctors) and color (pigments); improve their physicochemical properties, such as viscosity of the active ingredients (emulsifying, thickening, and anticaking agents); facilitate their elaboration (lubricants, diluents, binders, and isotonic agents) or conservation (desiccants, and opacifiers); and facilitate liberation of the active ingredient within the organism (disintegrants and carrier releasers). Within the clay minerals exhibiting planar structures, *kaolinite*, *halloysite*, and *montmorillonite* are the most studied in regard to applications on pharmacy and cosmetics, and within the clay minerals exhibiting nonplanar structures, *sepiolite* and *palygorskite* are the most studied too regarding the applications on pharmacy and cosmetics.

López-Galindo et al. (2011) produced an interesting article that we consider a landmark on the pharmaceutical and cosmetic uses of fibrous clays, represented by two clay mineral species, *sepiolite* and *palygorskite*, which are characterized by the fibrous habit of their crystals and particles.

Attapulgite is a commercial name frequently used instead the scientific name *palygorskite*. The name *attapulgite* was introduced by De Lapparent in 1935 for fibrous clay formed near Attapulgus, Georgia, USA, a name that was discredited by the International Mineralogical Association (IMA) because the name *palygorskite* had been attributed to the same type of mineral with occurrence in Palygorsk Range, Ural Mountains, Russia, i.e., in terms of minerals nomenclature precedence is a decisive factor.

López-Galindo et al. (2011) report relevant information on mineralogy, chemistry and crystal habit or shape of fibrous clay minerals, pharmaceutical and cosmetic nomenclature and specifications, use as active substances (as antidiarrheals and antacids and as adsorbents and protectors) and as excipients (as solid dosage forms and as liquid and semisolid dosage forms), drug interactions, use in cosmetics, and health risks.

The nomenclature of fibrous clay minerals is far from being uniform. López-Galindo et al. (2011) state that, for instance, the British Pharmacopoeia (2009) defines *palygorskite* as an "attapulgite," a purified native hydrated magnesium aluminum silicate, basically consisting in the clay mineral *palygorskite*, and defines "activated attapulgite" as the product of the controlled calcination of attapulgite to increase its adsorptive capacity.

The US Pharmacopoeia USP 32-NF 27 uses the name "attapulgite" in cosmetic formulations. In European Pharmacopoeia (EP 6.0, 2008) there is not any entry for "attapulgite."

Regarding *sepiolite*, its name is not found in any pharmacopoeia, although it is named "magnesium trisilicate." However, those pharmacopoeias referred to contain the technical specifications required for the products "attapulgite," "activated attapulgite," and "magnesium trisilicate."

Some other authors have produced relevant scientific information on pharmaceutical formulations, including fibrous clay minerals for medical applications: Hermosin et al. (1981), Fang (1988), Ueda and Hamayoshi (1992), Cerezo et al. (2001), Viseras et al. (2001), Zhang et al. (2004), Uhlen et al. (2004), López-Galindo and Viseras (2004), Hu et al. (2006), Changbing et al. (2008), and Zhang et al. (2009).

Gálan and Singer (2011) are the editors of an excellent book on new developments in *palygorskite* and *sepiolite* research that deals with geology, mineralogy, genesis, and environmental applications.

9.1.1 Skin Anatomy, Physiology, and Pathways for Mineral Permeance

In cosmetics as in pharmaceuticals the understanding of the interaction between minerals and human skin requires the best and updated knowledge of both essential properties of minerals and skin.

According to Viseras et al. (2019), the skin, in terms of anatomy and physiology, plays two fundamental functions: temperature control and barrier against physical, chemical, and thermal aggressions. Also, the skin is characterized by a multilayered structure: the *epidermis* (outer layer making contact with the exterior being 0.05 to 1.55 mm thick, the maximum value on hand palms and feet soles, and it is multistratified too, divided into five strata; the *stratum corneum (SC)* being the inner strata which determines the permeation and control of drugs); the *dermis* (real cellular layer, much thicker than the epidermis, with blood vessels, nerves, hair follicles, and sebaceous and sweat glands); and the *hypodermis* (inner layer, conditioning energy supply and thermal insulation).

In an adult human, the skin measures in average 1.8 m^2. *SC* is the hardest barrier of the skin and comprises rows of *corneocytes* (matured *keratinocytes* organized on a "brick and mortar" structure), corneocytes being the "bricks" immersed in a lipid matrix corresponding to the "mortar."

Very recently Carbajo and Maraver had analyzed the existing cutaneous absorption and desorption models, particularly of the polar and hydrophilic solutes, the case of minerals in ionic form, assumed to be the most therapeutically relevant in balneotherapy. When intact, *SC* is practically impenetrable to ions, but this characteristic could be partially modified according to exogenous or endogenous circumstances.

Wang et al. (2007) applied the "brick and mortar" model to predict the skin's permeability of hydrophilic and hydrophobic solutes through the diffusion coefficient solutes in free water. This model served to predict the skin' permeability of hydrophobic solutes but was unable to effectively predict the permeability of hydrophilic solutes (Chen et al. 2010; Wang et al. 2007).

Chen et al. (2010) applied too the "brick and mortar" model according to the intracellular cement absorption route, the transcellular route; published data on the binding capacity of the different solutes to lipids, *SC* keratins; and obtained accurate predictions about hydrophilic solutes for the lipid-corneocyte interface. Human *SC* has between 10 and 20 layers of keratinocytes embedded in a continuous intercellular lipid matrix.

Several authors have proposed models to predict skin permeability, the four-pathway model of Mitragotri (2003) and the "corneal brick and mortar model" of that with the "brick and mortar model" of Wang et al. (2007) and Chen et al. (2010) being the ones deserving preference.

Mitragotri et al. (2011) have considered corneocytes to be impermeable and examined the skin permeability of hydrophilic solutes through pores formed in the intercorneocyte cement, and in the Mitragotri four-pathway model, two pathways were applied to lipophilic compounds by free diffusion and lateral diffusion of lipids in the intercorneocyte cement, the other two being applied to hydrophilic compounds through intercorneocyte pores and shafts embracing sweat glands, hair follicles, and sebaceous glands.

There are two pathways or routes for the transdermal penetration of inorganic and organic elements and compounds:

1. *Transappendageal* – Via pores and shafts embracing sweat glands and hair follicles with their associated sebaceous glands; minor overall penetration, although preferred for ions and large polar molecules because the *SC* is not involved.
2. *Transepidermal* – Via diffusion through the *SC*; it is the dominant pathway and comprises two routes: *transcellular* also known as *intracellular* and *intercellular*.

The *intracellular route* is preferred for hydrophilic molecules, whereas the *intercellular route* is preferred for both hydrophilic and lipophilic molecules (these in particular), which have to diffuse via a tortuous route within the continuous lipid domain. An active molecule that penetrates the *SC* can reach the dermis and enter the bloodstream.

About skin anatomy, physiology, and permeation routes see Viseras et al. (2019), Prow et al. (2011), and Fig. 9.1.

9.1.2 Skin Conditions

Human skin can show several types of disorders described as follows:

Dermatitis A general term for inflammation of the skin; atopic dermatitis (a type of eczema) is the most common form.

Eczema Skin inflammation (dermatitis) causing an itchy rash; most often, it's due to an overactive immune system.

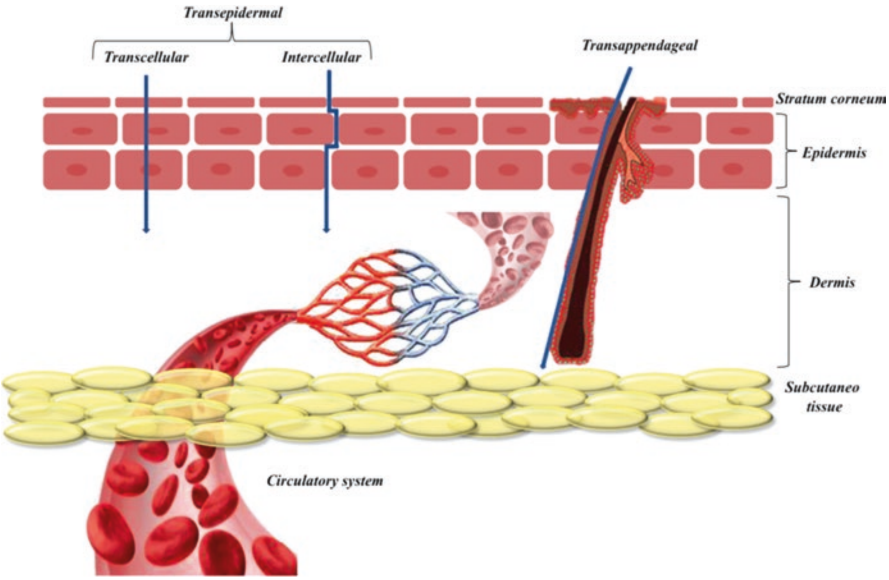


Fig. 9.1 Skin layers and the diverse routes for skin permeability. (Viseras et al. 2019)

Psoriasis An autoimmune condition that can cause a variety of skin rashes; silver, scaly plaques on the skin are the most common form.

Dandruff Scaly condition of the scalp may be caused by seborrheic dermatitis, psoriasis, or eczema.

Acne The most common skin condition; acne affects over 85% of people at some time in life.

Cellulitis Inflammation of the dermis and subcutaneous tissues, usually due to an infection; a red, warm, often painful skin rash generally results.

Skin Abscess (Boil or Furuncle) Localized skin infection that creates a collection of pus under the skin; some abscesses must be opened and drained by a doctor in order to be cured.

Rosacea A chronic skin condition causing a red rash on the face; *rosacea* may look like acne and is poorly understood.

Melanoma The most dangerous type of skin cancer; melanoma results from sun damage and other causes; a skin biopsy can identify melanoma.

Seborrheic Keratosis Benign, often itchy growth that appears like a “stuck-on” wart; seborrheic keratoses may be removed by a physician, if bothersome.

Walters and Roberts (2019) in Chap. 2 of the book entitled *Cosmetic Formulation: Principles and Practice* describe pretty well the skin's morphology, development, and physiology.

9.2 Minerals Utilized in Pharmacy

Pharmacy is currently defined as the art and science of preparing, preserving, compounding, and dispensing medicines or remedies. The word *pharmacy* is most likely taken from the Greek word *pharmakon*, which means both remedy and poison.

Minerals have been used since the first civilizations, Mesopotamian and Egyptian, either as remedies or as poisons. In fact, there are several minerals, defined as natural, inorganic, and crystalline solids, that participate in formulations of drugs with active or excipient functions, highlighted in items 9.2.1 and 9.2.2 of this chapter.

Excipients are the largest constituents (up to 95%) of the medicines and play fundamental roles in what concerns drug release and bioavailability. Clays and clay minerals account for ~5% of the global market for inorganic excipients (Viseras et al. 2019).

Much of the following information is updated from the relevant information available in the book *Applied Mineralogy: Health and Environment* by Carretero MI and Pozo M (2007) and in the article "Clays, Drugs, and Human Health" by Carretero et al. (2006).

Also, adequate and relevant information has been available in scientific articles published by the following authors: Gálan et al. (1985), Veniale (1992, 1997), Viseras and López-Galindo (1999, 2000), Carretero (2002), Cerri et al. (2004), López-Galindo and Viseras (2004), Zhang et al. (2004, 2009), Carretero and Pozo (2007, 2009, 2010), Carretero et al. (2006), Droy-Lefaix and Tateo (2006), Del Hoyo (2007), Lefort et al. (2007), Aguzzi et al. (2007, 2016), López-Galindo et al. (2011), Khurana et al. (2015), Sandri et al. (2016), Awad et al. (2017), Moraes et al. (2017), Carazo et al. (2018), Hernández et al. (2019), and Viseras et al. (2007, 2010, 2015, 2019).

The publications referred to deal with the use of minerals for internal and external or topical applications in pharmacy, cosmetics, and medicine, most of the minerals being clays and clay minerals.

Carretero et al. have identified the clay minerals used as active ingredients in pharmaceutical products, the administration methods (orally and/or topically), as well as the therapeutic activity and the cosmetic action. The authors show too the physical and physicochemical properties as well as the functions for which the clay minerals are used as active ingredients and as excipients in pharmaceutical and cosmetic products.

9.2.1 Minerals as Active Substances in Pharmaceuticals

Gastric Antacids Reduce, by neutralizing effect, the so-called gastric acidity created in the stomach by the hydrochloric acid (HCl) produced in it, since it promotes a rise in pH from 1.5–2 to 3–4. The minerals most used for this purpose are *calcite*, $CaCO_3$; *magnesite*, $MgCO_3$; *gibbsite*, $Al(OH)_3$; *brucite*, $Mg(OH)_2$; and *hydrotalcite*, $Mg_6Al_2(CO)_3(OH)_{16}$, which participate in the composition of tablets, suspensions, and powders. *Sepiolite,* a fibrous clay mineral that in pharmacopoeias is identified as *magnesium trisilicate,* is used in therapeutic formulations in the form of either suspensions or tablets recognized by its antacid function, both used in oral administration. *Palygorskite,* also a fibrous clay mineral identified as *attapulgite* in pharmacopoeias, based on its adsorbing capacity is used in therapeutic formulations associated with some drugs and in the form of either suspension or tablet is recognized by its antidiarrheal and antacid functions, both used in oral administration. The antidiarrheal potential is attributed to the ability to adsorb toxins and pathogenic bacteria and to the increase of both volume and consistency of the gastrointestinal content.

Sepiolite and *palygorskite* can have two functions: (1) adsorbent coating for toxins and bacteria in the gastrointestinal tract and (2) protective coating for both the stomach and intestine, more effective in the case of *sepiolite*. On these subjects several studies have been carried out, identified in the article entitled "Pharmaceutical and Cosmetic Uses of Fibrous Clays" by López-Galindo et al. (2011).

Carretero et al. (2013) had identified the clay minerals used as active ingredients in pharmaceutical products, the administration methods (orally and/or topically), and the therapeutic activity as well as the cosmetic action.

Gastrointestinal Protectors Certain minerals can prevent the contact between gastric enzymes and gastrointestinal mucosal cells. The minerals most used for this purpose, which must have high specific surface area (SSA) and high adsorption/absorption capacity, are as follows: *gibbsite*, $Al(OH)_3$; *kaolinite*, $Al_2Si_2O_5(OH)_2$; *sepiolite*, $Mg_8Si_{12}O_{30}(OH)4(OH_2)_4.8H_2O$; and *smectites* represented by the species: *montmorillonite* $(Al_{1.67}Mg_{0.33})Si_4O_{10}(OH)_2M^{+0.33}$; *saponite*, $Mg_3(Si_{3.67}Al_{0.33})O_{10}(OH)_2M^{+0.33}$; and *hectorite*, $(Mg,Li)_3(Si,Al)_4O_{10}(OH)_2M^{+0.33}$, M representing the exchangeable cations, Na^+ and Ca^{2+}, the most common.

By adhering to the gastric and intestinal mucous membranes, the aforesaid minerals can enhance the thickness of the mucus barrier, diminish irritation and gastric secretion, and adsorb or take up gases, toxins, bacteria, and even viruses (Droy-Lefaix and Tateo 2006).

Antidiarrheics Decrease stool flow and stool frequency, manifestations that are characteristic of diarrhea, the main causes of which are bacterial infection and intoxication. The most used minerals are *kaolinite*, *palygorskite*, *sepiolite*, and *smectites*, all clay minerals characterized by high specific surface area (SSA) and adsorption capacity.

In particular are *palygorskite* $(Mg,Al,Fe^{3+})_5(Si,Al)_8O_{20}(OH)_2(OH_2)_4.(H_2O)_4$ and *sepiolite* $Mg_8Si_{12}O_{30}(OH)_4(OH_2)_4(H_2O)_8$, clay minerals whose crystalline fibrous habits and structure have the ability to retain liquids between the fibers.

Laxatives Promote defecation and are used orally, and their purgative effect results from osmotic action or irritation of the intestine. The most used minerals are sodium and magnesium compounds, such as *mirabilite*, $Na_2SO_4.10H_2O$, and *epsomite*, $MgSO_4.7H_2O$.

Antianemics Combat the iron deficiency necessary for the formation of hemoglobin. The most used mineral is the *melanterite*, $FeSO_4.7H_2O$, a salt where the iron being in the ferrous state, Fe^{2+}, is easily soluble and the solution is used orally.

Antiseptics and Disinfectants Inhibit the growth or the elimination of pathogenic microorganisms on human body internal and external surfaces. The most used minerals as antiseptics and disinfectants are *sulfur* (S), *borax* ($Na_2B_4O_7$), *zincite* (ZnO), and *alum* $KAl(SO_4)_2 12H_2O$.

Dermatological Protectors Provide the skin protection against aggressive external agents. The most used minerals are *kaolinite*, $Al_2Si_2O_5(OH)_2$; *talc*, $Mg_3Si_4O_{10}(OH)_2$; *zincite*, ZnO; *anatase*, TiO_2; *rutile*, TiO_2; and *smectites*.

Solar Protectors Being also cosmetic products, they reflect to a lesser or higher degree the ultraviolet radiation and in the form of creams prevent the formation of burns. The most used minerals are *anatase*, TiO_2; *rutile*, TiO_2; and *zincite*, ZnO. Nowadays, *anatase* and the *zincite* are replaced by the synthetic equivalent, white, with a high refractive index ($n = 2.70$), in the form of nanoparticles (0.05 μm) and not degraded by light.

Cosmetics Adhere easily to the skin forming protective films when they are used in the form of creams or powders, attenuating imperfections and shine and absorbing grease, toxins, etc. The most used minerals are *talc*, *kaolinite*, *smectites*, and *sepiolite*. Minerals belonging to the *micas group*, *muscovite* $KAl_2(Si_3,Al)O_{10}(OH)_2$ and *lepidolite*, are used in eye shadows and lip paint to produce iridizations and glitters. Other still minerals, such as *halite*, NaCl; *sylvite*, KCl; *epsomite*, $MgSO_4.7H_2O$; and *mirabilite*, $Na_2SO_4.10H_2O$, are used in bath salts.

Abrasives and Mitigators of Dental Sensitivity Being also cosmetic products, they act as soft abrasives and polishers in toothpastes, examples of which are the abrasive and polishing effects of *calcite*, $CaCO_3$, in formulations of toothpastes, or as attenuators of dental sensitivity in the case of Chile's *nitro* or potassium nitrate, KNO_3.

Ocular Congestion Relief Included in isotonic eye drops, mineral *halite* NaCl solutions produce a decongestant and antiseptic effects, for example, if you suffer from eye irritation, and ocular dryness.

Mineral Supplements They can suppress dietary deficiencies in terms of vitamins and minerals. Naturopathologists believe that the state of good health depends on three main factors: structural, biochemical, and psychological. Naturally it is in the biochemical factor that the minerals and mineral supplements intervene.

In mineral supplements, minerals participate in the formulations of many drugs, not in the elemental form but in inorganic or organic salts (e.g., *potassium chloride*, *manganese sulfate*, *potassium iodide*, *chromium chloride*, *sodium molybdate*, *nickel sulfate*, *sodium metavanadate*, *sodium selenate*, *dibasic calcium phosphate*, *ferrous fumarate*) or in oxides such as *cupric oxide*, *zinc oxide*, *manganese oxide*, and *silicon dioxide*.

In humans the absorption and incorporation of minerals takes place in the gastrointestinal system, predominantly in the duodenum and in the first part of the jejunum.

Immobilizers in Orthopedics and Molds in Odontology The *gypsum*, $CaSO_4.2H_2O$, finely ground and calcined at 150 °C to convert to the hemihydrate form, $CaSO_4.1/2H_2O$, which in the construction industry is called "stucco plaster" or "plaster of Paris," is used in dentistry in the manufacture of dental molds and also in traumatology for the immobilization of fractured limbs. The hemihydrate has the ability to absorb water and, crystallizing, hardens preserving the shaped form.

Contrasting Means in Disease Diagnosis The mineral *magnetite*, $FeFe_2O_4$, and the mineral *maghemite*, ϒ Fe_2O_3, due to their magnetic properties are used after being finely ground as contrasting agents in diagnostic techniques, as is the case of magnetic resonance.

Means of Diagnosis and Treatment The mineral *barite*, $BaSO_4$, because it has a very high density and is opaque to X-rays, when finely ground and associated with *smectite* and in the form of colloidal suspension, is used as a radiological contrast agent in examinations of the intestinal tract.

Hemostatic Agents It is well known that wounds caused by accidents and surgeries produce vascular damages and skin breakdown which facilitate hemorrhages, microbial invasion, and infection.

Some cationic clay minerals can act as antihemorrhagic agents due to their high swellability and capacity for water and other liquid absorption, such property leading to the formation of a paste-like substance when the minerals come into contact with blood or body fluids, thereby acting as a bleeding barrier with strong adhesiveness to the surrounding tissues.

Awad et al. (2017) point out the *kaolinite* properties that could favorably intervene in the coagulation mechanism creating a physical mesh which facilitates platelet aggregation and coagulation (Glick et al. 2013). Experience shows that the application of *kaolinite* as topical hemostatic agent helps in accelerating the formation of clots of blood, the blood clotting potential being very much influenced by the negatively charged *kaolinite* particle surfaces at the pH of blood and human plasma

(Smith et al. 2013; Glick et al. 2013). *Kaolinite* is a component of common wound dressing commercial products.

Commercially, *zeolite*, *smectite*, and *kaolinite* are sold as absorbents and to promote clotting of bleeding arteries. According to Baker et al. (2007) when *dry zeolite* is hydrated, it produces enough heat (~100 °C) to cauterize blood vessels, but unfortunately it causes severe damage to vascular tissue, requiring post-trauma grafting. The use of *smectite* on wounds has also proven problematic. But new products such QuikClot® and Combat Gauze™ have been introduced in the market (Ghadiri et al. 2014). These products can be considered medical devices rather than medicines.

QuikClot® gauze is a wound dressing gauze impregnated with *synthetic zeolite*, a microporous alumina-silicate with high adsorptive capacity that acts as molecular sieve and adsorbs water. The adsorption of water along with trapping of platelets within the micropores leads to concentration of clotting factors and platelets and promotes clot formation. Heavy bleeding that occurs when femoral arteries are severed can be stopped using ground up and sterilized zeolite (Alam et al. 2004).

Combat Gauze™, a nonwoven gauze impregnated with *kaolin*, has replaced other clay-based hemostatic dressing products and is the only product endorsed for use in the first-line treatment of life-threatening injuries. *Kaolin* is effectively known for its capabilities to induce and accelerate blood clotting. In April 2008, the US Naval Medical Research Institute announced the successful use of a kaolinite-derived aluminosilicate infusion in traditional gauze, known commercially as QuikClot Combat Gauze, which is still the hemostat of choice for all branches of the US military.

In a recently published study (Gaharwar et al. 2014), *laponite* and gelatin nanocomposites were formulated as an injectable hydrogel for hemorrhage treatment, a hydrogel that has displayed enhanced in vitro and in vivo coagulation properties.

9.2.2 Minerals as Excipients in Pharmaceuticals

Certain minerals, particularly clay minerals such as *kaolinite*, smectites, *talc*, *palygorskite*, and *sepiolite*, as a consequence of their physical and physicochemical properties, are used worldwide as inactive components in non-parenteral administration, i.e., as excipients in pharmaceutical formulations having the following aims:

1. To improve the organoleptic characteristics of the formulation, such as taste and color, through the incorporation of flavor-correcting minerals and chromatic pigments.
2. To improve the physicochemical characteristics of the formulation, such as viscosity and suspensibility of the active substance, through the incorporation of minerals with thickening and emulsifying action.
3. To facilitate preparation of the formulation through the incorporation of minerals with lubricating action and diluent.

4. To facilitate preparation of the formulation through the incorporation of minerals with desiccant action and facilitate the release of the active substance into the body through the release-carrying minerals of that substance.

Mineral excipients can be used both in solid dosage forms and liquid and semisolid dosage forms (López-Galindo et al. 2011). For instance, *palygorskite* and *sepiolite* can be used, both in the powder form, as fillers (diluents, disintegrants, and absorbents) and as suspending agents in mixtures of components to prevent their settling and separation. Dispersed systems important in both pharmaceutical and cosmetics include liquid forms (suspensions and emulsions) and semisolid forms (ointments, creams, and gels).

Lubricants *Talc* which is a magnesium-rich phyllosilicate, due to the easy and perfect cleavage of its crystals due to the weakness of the chemical bonds (of the van der Waals type) existing between the structural layers, justifies the sensation of unctuousness to the touch and provides a lubricating effect which facilitates, for example, the preparation of tablets, avoiding the adhesion of the powders to the pistons, and facilitating the compacting of the same powders.

Taste Correctors The clay minerals *smectite*, *palygorskite*, and *sepiolite* by having high absorption capacities can be incorporated into some orally administered pharmaceutical formulations to mask the unpleasant taste of certain active substances in them.

Disintegrants Disaggregating or disintegrating of minerals into much smaller particles facilitates and promotes in solid formulations the rapid dissolution of the active ingredients to be absorbed, for example, in the gastrointestinal tract after oral administration.

The *smectite*, *palygorskite*, and *sepiolite* clay minerals, and *calcite* ($CaCO_3$) and *magnesite* ($MgCO_3$) minerals, can be incorporated into certain orally administered formulations in the form of tablets, which have to be disintegrated in the stomach and small intestine in order for the active substance to be released and act therapeutically. The disintegrating action of smectites is due to the swelling or expansion property by absorbing water in the spaces between structural layers and by being decomposed in the strongly acid medium ($pH = 2$) of the stomach.

Palygorskite and *sepiolite* favor disintegration because their fibers readily disperse in the aforementioned medium. In turn, the adsorbing power of *calcite* and *magnesite* results from being soluble in acidic medium.

Diluents Various clay minerals such as *smectites*, *palygorskite*, *sepiolite*, *kaolinite*, and *talc* are used as diluents in pharmaceutical formulations in order to dilute active substances of organic nature until the appropriate dose is obtained. The diluent may also facilitate the compaction of powders and granules.

Calcite and *magnesite* carbonates may be incorporated into the formulations in predetermined doses to modify the pH to alkaline values. The clay minerals smectite and kaolinite are used as thinners in cosmetics.

According to Awad et al. (2017), the choice of a proper diluent depends basically on the hydrophobicity and bioavailability of the active component. The minerals referred to are water-soluble, the reason why the choice of diluents for mineral powders is commanded by powder fineness, moisture or loss on drying, hardness, friability, compressibility, physical and chemical stability of the final pharmaceutical product, and drug release profile.

Binders ***or Agglomerants*** Binders are components added during the blending process of formulation ingredients, which are needed to bind and cover all ingredients important for granulation, tableting, or encapsulation processes.

Kaolinite and *montmorillonite* mixed with appropriate polymers are known as good binders.

Pigments Mineral pigments are used to modify the color of the formulation when this exhibits unattractive color, or the pigment is convenient for the identification of a medicine among others. They can provide significant opacity when the active substance is photosensitive.

Red iron oxide called *hematite* (Fe_2O_3), the black iron oxide called *maghemite* (Fe_2O_3), and the yellow iron hydroxide called *goethite* (FeOOH) are examples of the most commonly used mineral pigments.

Desiccants The mineral *anhydrite* ($CaSO_4$) is an example of a desiccant because it avoids the acquisition of moisture by the pharmaceutical formulation, thus favoring its conservation and avoiding the disintegration of the preparations when in the form of compacted powders (tablets) or granules.

Emulsifiers and Thickeners The colloidal character, as well as the *viscosity* and *thixotropy*, properties that some *clay minerals* may exhibit, causes them to be used as emulsifying and thickening agents in certain pharmaceutical formulations in which the solid components are dispersed in a liquid phase to be administered orally or topically.

Smectites, *palygorskite*, *sepiolite*, *kaolinite*, and *talc* are the clay minerals used to avoid segregation of the components of the said formulations with the consequent formation of sediment. For this purpose, also minerals such as *halite* NaCl and *sylvite* KCl may modify the viscosity of the dispersions due to the strongly ionic character of the said minerals.

Flavor Correctors *Smectites*, *palygorskite*, and *sepiolite* are the main clay minerals used as flavor correctors due to their high SSA (specific surface area) and high adsorption capacity. In spite of their comparatively lower SSA and adsorption capacity, *kaolinite* and *talc* can be part of pharmaceutical formulations, to mask the unpleasant flavor or taste of certain active ingredients that must be administered orally.

Carriers for the Controlled Release of Drugs Clay-based systems have been developed, particularly in the last 10–12 years, as carriers adequate for controlled release of drugs (antibiotics, anticancer, antibacterial, antimycotic, antifibrinolytic, antioxidant, anti-inflammatory, etc.), as an alternative strategy to the conventional immediate-release dosage forms. Such systems include *natural clay minerals* (e.g., *halloysite*, *kaolinite*, *montmorillonite*, *sepiolite*, and *palygorskite*), *synthetic clay minerals* (e.g., *layered double hydroxides*, *LDHs*, and *Li-fluorohectorite*), and *clay mineral-polymers composites*, *clay-polymer hydrogels and films*, and *clay-polymer nanocomposites* (Viseras et al. 2010; Rodrigues et al. 2013; Yu et al. 2013; De Sousa et al. 2013; Sironmandi 2015; Hári et al. 2016; Hernández et al. 2018; Pierchala et al. 2018; Viseras et al. 2019). Even the clay minerals above referred to, which are essential components of the solid part of healing mud / peloid of both therapeutic and cosmetic typology, whenever used in topical applications, can be considered carriers of the active substances, elements and/or compounds exiting in the liquid phase, and that could be free in solution or reversibly adsorbed at the clay mineral surfaces.

New pharmaceutical products are developed to control the release of drugs, to enhance drug water solubility, to improve drug dispersibility, and to improve skin drug absorption.

According to Ghadiri et al. (2014), two methods of clay-drug hybridization are known, namely:

1. In solution intercalation, where the clay mineral is dispersed in solubilized drug solutions followed by equilibration and finally subjected to recovery by drying in the solid.
2. In situ melting intercalation, where clay mineral and drugs are both maintained at the melting temperature of the drug.

The utilization of clay minerals in modulating drug bioavailability began with studies which showed a decrease of drug oral absorption upon co-administration with clay minerals. Since this discovery the intercalation of cationic drugs in *cationic clay minerals* has been successfully employed to prolong the therapeutic action of such drugs (Ghadiri et al. 2014).

Clays, nanoclays, and more precisely organoclays, as well as zeolites can be used, for instance, as topical delivery agents for various antimicrobial products. Chlorhexidine intercalated into montmorillonite was found to be useful in skin pathologies due to its successful inhibition of the growth of a wide range of microorganisms including both *Staphylococcus aureus* and *Escherichia coli* (Saha et al. 2014). Also, an organo-modified *bentonite* used for gentamicin topical application was developed with sustained bactericidal activity and enhanced drug permeation rate (Iannuccelli et al. 2018). Yet, one non-bactericidal commercial *kaolin* could be turned bactericidal in order to be used as an anti-infectious ointment for the treatment of infectious skin disorders, an ointment that could incorporate specific antibiotics to treat specific skin bacteria (Gomes et al. 2019).

A Zn^{2+}-bearing micronized zeolite has been charged with erythromycin to investigate the antimicrobial efficacy against erythromycin-resistant *Propionibacterium* strains, and a 99.5% reduction in *Propionibacterium acnes* viability could be observed (Bonferoni et al. 2007; Cerri et al. 2004, 2006).

According to Ramasamy et al. (2017), the design of drug nanocarriers for controlling disease pathologies, either by drug enrichment at the diseased site or by controlling pathogens using novel therapeutic agents, has been prepared over the past 10 (ten) years, based on the so-called smart chemistry-based nanosized polymer-based drug delivery systems. Those nanocarriers are prepared from a range of inorganic and organic compounds, including polymers, lipids, carbon nanotubes, quantum dots, and mesoporous materials.

Wound Healing By definition wound healing is a complex and dynamic process of replacing devitalized and missing cellular structures and tissue layers. The wound healing process in an adult human can be divided into three or four distinct phases. Earlier authors reported the three-phase concept as inflammatory, fibroblastic, and maturation, which have also been named as inflammatory, proliferation, and remodeling, and this concept has been maintained by some authors. The four-phase concept consists of hemostasis, inflammatory, proliferation, and remodeling. In the three-phase approach, the hemostasis phase is contained within the inflammatory phase (Sorg et al. 2017).

The prevalence of diabetic disease and venous insufficiency leads to the increase of chronic wounds. The prevalence of ulcers significantly increases the total healthcare expenditure.

Zinc, silver, copper, and iron are the main minerals that participate in wound healing. Zinc-based products play a key role in protein and collagen synthesis, as well as in tissue growth and healing. Zinc deficiency has been associated with delayed wound healing, reduced skin cell production, and reduced wound strength. Silver-based products and traditional dressings have also been employed in wound care and are commonly used in most public healthcare systems. Silver is a broad-spectrum antimicrobial agent that is commonly used in the treatment of skin lesions, in particular, wounds and burns. Silver is one of the most commonly applied antimicrobial agents in wound care, being available as the active ingredient of diverse products, such as solutions (e.g., silver nitrate), creams and gauze dressings, and dressings (Pereira and Bártolo 2016).

Recently, clay minerals have been proposed in the biomedical field in tissue engineering as enhancers of cell attachment, proliferation, and differentiation (Dawson and Oreffo 2013; Naumenko et al. 2016) and also as antimicrobials (Williams et al. 2011; Gomes et al. 2019, 2020a, b).

Sandri et al. (2020) have designed and developed electrospun scaffolds, entirely based on biopolymers, loaded with *montmorillonite* or *halloysite* intended for skin reparation and regeneration. The scaffolds proved to possess the capability to enhance fibroblast cells' attachment and proliferation with negligible proinflammatory activity.

9.3 Minerals Utilized in Cosmetics

9.3.1 Basic Concepts

Since the dawn of civilization, cosmetic products have been routinely used for body care, and minerals were and still are constituents of such products. However, during the last few decades, there has been a big boost in the use of cosmetics. These include products such as care creams, powders, eye makeup, mouthwash, lipsticks, etc. It happens that the health awareness about the chance of having hazardous chemicals in cosmetics is drawing more and more attention from researchers and clinicians. Since cosmetics are applied in direct contact with the skin, dermal exposure is the most significant exposure route.

Clays and clay minerals are extensively used in cosmetics, for care and beauty purposes. The use of a particular clay or clay mineral for a specific cosmetic application depends on mineralogical composition, crystallochemical structure of the clay minerals, and chemical composition (Mattioli et al. 2016). Clays are necessary for the cosmetic industry since they present interesting characteristics such as easiness of application and removal, reduced time for drying and hardening, and dermatological innocuousness (Carretero, 2002; Toedt et al. 2005). Clay used as facial mask may be done directly on the skin at room temperature mixing, for instance, kaolinite-rich or montmorillonite-rich clay with water. But, to treat dermatological diseases, such as blackheads, spots, acne, and seborrhoea, it is recommended the application of warm clay/water mixture. The heat increases perspiration and sebaceous secretions, while it also opens the pilosebaceous orifices and activates the metabolic change and the excretion of catabolites (Carretero, 2002).

The available scientific information on clay dermatological applications is less than it should be. It is common to correlate clay color with dermatological indications. Just on an empirical basis, yellow clay is used against bacterial infections; red clay is used for skin cleansing; blue clay is effective against acne; green clay is used to reduce the amount of oil secreted by sebaceous glands; while black clay may be indicated for general skin nourishment (Mpuchane et al. 2010).

According to the Council Directive 76/768/EEC, the definition of *cosmetic product* is as follows:

> Any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning, perfuming, changing their appearance and/or correcting body odours and/or protecting or keeping in good condition.

On the other hand, the US Food and Drug Administration (FDA) define *cosmetics* as follows:

> Articles intended to be applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance.

The same US authority uses the term “cosmeceutical” to define “a product that fits the niche between a drug and cosmetics”; it has measurable biological action in the skin, like a drug, but is regulated as a cosmetic since it claims to affect appearance (e.g., antiaging and sunscreen products).

Also, the European Community Directive 2001/83/EC defines *medicinal product for human use* as follows:

> Any substance or combination of substances administered to human beings for treating or preventing disease, making a medical diagnosis or restoring correcting or modifying physiological functions.

In addition to the European Community Directive 2001/83/EC, the EC Regulation 1223/2009 that became fully applicable in 11 July 2013, establishes the safety information that must accompany different products (clays included) when commercialized in order to uniform the safety of cosmetics, better harmonize compliance within the member states, simplify procedures, and streamline terminology.

According to the European Commission Regulation No 1223/2009, a cosmetic product means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly of cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition, or correcting body odors.

Also, according to the EC Regulation 1223/2009, cosmetic products must not contain any of the substances listed in Annex II, substances that include heavy metals such as Pb, Cd, As, Sb, and their compounds as well as Hg and its compounds. The Article 17 of EC Regulation 1223/2009 states that the unintended presence of heavy metals in cosmetics is only allowed if it is technically unavoidable under good manufacture practices and if the products are still safe for the human health.

Bund (2017) says that potential heavy metal contaminations can be expected particularly in cosmetic products containing high levels of inorganic or mineral components, especially powders and cream products, decorative cosmetics, and toothpastes.

Ullah et al. (2017) made a comparative study of heavy metal content in 15 cosmetic products, both imported and locally manufactured and marketed in Khyber Pakhtunkhwa, in Pakistan. The authors have identified high concentrations of Fe, Zn, Pb, and Cu and concluded that prolonged use of such products coating the elements referred to could pose threat to human health.

In cosmetic products in general (makeup, rouge, eye shadow, eyeliner, etc.), concentration limits for Pb, Cd, Hg, As, and Sb should be lower than 2.0, 0.1, 0.1, 0.5, and 0.5 mg.kg^{-1}, respectively.

The SCCS (Scientific Committee on Consumer Safety) is mandated to propose revisions to the Regulation 2009/1233/EC, called "SCCS Notes of Guidance for the Testing of Cosmetics and their Safety Evaluation," the 9th revision SCCS/1564/15 being in 29 Sept. 2015. Also, the Occupational Safety and Health Administration (US Department of Labor, OSHA CFR 1910–1200) establishes the safety information that must accompany different commercial products (clays included). Such information referred to must include the following items: accurate identification of the substance; the main intended or recommended uses; composition/information on ingredients; hazards identification, handling, and storage; physical and chemical properties; stability and reactivity; and toxicological information.

To be suitable for pharmaceutical or cosmetic applications, clays must comply with a number of chemical (stability, purity, chemical inertia), physical (texture, particle size, water content), and toxicological (toxicity, safety and microbiological purity) requirements (López-Galindo and Viseras 2004; Viseras et al. 2007). Specifically, clays must have zero or very low toxicity.

Mattioli et al. (2016) have determined the suitability of 15 (fifteen) commercial clay samples available on the market and used for cosmetic purposes based on textural, mineralogical, and chemical analyses. The authors have determined that some of the studied samples show potential risks to human health.

9.3.2 Cosmetic Ingredients

In the manufacture of cosmetics, thousands of chemicals can be used. A typical cosmetic product contains anything from 15 to 50 ingredients, most not being minerals.

Polefka et al. (2012a, b) produced a very interesting article on a literature survey of the interaction of mineral salts with the skin. The authors state that there is growing scientific evidence of their health effects. Well-being and the attractiveness of the skin are strongly influenced by nutrition.

Early in 2011, the US Department of Health and Human Services and the Department of Agriculture issue the Dietary Guidelines for Americans in which 9 (nine) minerals and 12 (twelve) vitamins were recognized as essential. The minerals include calcium, copper, iron, magnesium, phosphorous, zinc, potassium, sodium, and selenium. The survey attempts to summarize what has been published in the literature on the interaction with the skin of eight of the nine essential elements referred to. Phosphorous was not analyzed in the survey.

Most cosmetics contain a combination of at least the following ingredients: water, emulsifier, preservative, thickener, emollient, color pigment, fragrance, and pH stabilizer.

Water Water constitutes the basis of almost every type of cosmetic product, creams, lotions, makeup, deodorants, shampoos, and conditioners.

Water, distilled, or purified, in order to be free of microbes, toxins, and other pollutants, is used in cosmetic formulations and plays an important part in the process, often acting as a solvent to dissolve other ingredients and forming emulsions for consistency.

Emulsifier Emulsifiers are the ingredients that help to keep unlike substances, such as oil and water, from separating.

Emulsifiers are added to change the surface tension between the water and the oil, producing a homogeneous and an even texture of cosmetic. Examples of emulsifiers include polysorbates and potassium cetyl sulfate.

Preservative The mineral salt, halite (NaCl), has been used as an antibacterial agent and as a food preservative for millennia.

In cosmetics preservatives are added to them to extend their shelf life and prevent the growth of microorganisms, such as bacteria and fungi, which can spoil the product and possibly harm the user. Since most microbes live in water, the preservatives used need to be water-soluble.

Preservatives used in cosmetics can be both natural and synthetic. Some preservatives require low levels of concentration around 0.01%, while others require high levels as high as 5%. Some of the more popular preservatives include parabens, salicylic acid, formaldehyde, and tetrasodium EDTA, particularly utilized in cosmetics.

Parabens are derived from the parahydroxybenzoic acid (PHBA) and are the most widely used preservative in cosmetic products; they are very good in keeping the products mold and bacteria free and are also cost-effective.

Triclosan (TCS) is a chemical and broad-spectrum antimicrobial agent widely used and incorporated in cosmetics mainly as a preservative, to stop bacteria from growing on the product and spoiling it. It is also used as a biocide in many other personal care products such as deodorants, toothpastes, dentifrice gels, soaps, and shower gels. Toxic effects have been identified that could result from the extensive use of TCS-containing products, since its molecule could contribute to endocrinal system disruption, especially thyroid gland and male reproductive endocrinal system (Veldhoen et al. 2006; Wang and Tian 2015; Kumar et al. 2009). Triclosan could end up as contaminant in surface waters (Bedoux et al. 2011). Hence, the convenience of using natural antimicrobial preservatives based, for instance, on clay-reduced metals (Sect. 6.5 of this book).

Thickener Thickeners provide to cosmetic products an appealing consistency, and they can come from four different chemical families: lipid thickeners, naturally derived thickeners, mineral thickeners, and synthetic thickeners.

Emollient Emollients are some natural and synthetic chemicals including beeswax, olive oil, lanolin, mineral oil, glycerine, *zinc oxide*, and diglycol laurate that help to keep skin soft by preventing water loss.

Color Agent/Pigment In cosmetics the color agents/pigments can modify a person's natural skin coloring. Pigments can be classified into two main categories: organic, which are carbon-based molecules, and inorganic, which are in general metal oxides, mostly *flakes*, which comparatively to the organic pigments are usually duller, although more resistant to heat and light and able to provide longer-lasting color, occurring as minerals such as *iron oxide*, *manganese oxide*, *chromium oxide*, and *mica.*

Other natural colors can come from plants such as beet powder or from animals like the cochineal insect that is used in red lipsticks and referred to as *carmine*.

Glimmer and Shine In cosmetics glimmer and shining can be provided by some materials, the most common being mica and bismuth oxychloride. Cosmetic mica, as a rule, comes from *muscovite*, $KAl_2(AlSi_3)O_{10}(OH,F)_2$, also known as *white mica*.

Mica flaky particles are crushed up into fine powders (50–500 μm) that provide the shimmering effect common in many cosmetics. Mica coated with titanium dioxide (*rutile* and *anatase*) gives a whitish appearance when looked at straight on, but then produces a range of iridescent colors when looked at from an angle. Bismuth oxychloride creates a silver-grey pearly effect and is usually produced synthetically.

Fragrance *Fragrances* provide pleasant smells to the cosmetics, the smell being one of the key factors in a consumer's decision to purchase and/or use a cosmetic. Fragrances are chemicals, either natural or synthetic.

pH Stabilizer pH stabilizers provide the stability of cosmetic formulations.

As concluding note, it matters to emphasize how biotechnology could play a paramount role for the development of high-quality ingredients, safe and effective in cosmetics and aesthetic medicine (Pandey et al. 2015). About this subject, Gomes et al. (2020a, b) provide examples of those ingredients, such as hyaluronic acid, kojic acid, resveratrol, and enzymes, which are used in skin antiaging products, as well as of growth factors such as algae, stem cells, and peptides to be included in cosmetics and aesthetic medicines. The authors describe the most active ingredients that are produced from biotechnological processes.

9.3.3 Minerals as Excipients in Cosmetics

Some minerals can be incorporated as excipients in various cosmetic products, such as sunscreens, toothpastes, creams, powders, bathroom salts, and deodorants (Carretero and Pozo 2010).

Sunscreens Sunscreens are widely used to protect the skin from the harmful effects of sun exposure.

Zinc oxide (ZnO), corresponding to the mineral *zincite*, and titanium dioxide (TiO_2), corresponding to mineral polymorphs *anatase* and *rutile*, which are the most effective approved mineral-based forms, particularly of TiO_2 minerals, forms a good ingredient which protects the skin from sun damage. The synthetic analogs make a barrier on the skin which is able to reflect UVA and UVB rays avoiding their penetration down to the deep layers of the skin.

Minerals used as solar protectors must have high refractive indices and good light-scattering properties. The main drawback of the traditional or conventional sunscreens manufactured when those minerals are applied is the white chalky layer left on the skin. However, nanotechnology innovation makes feasible the use of sunscreens products based on nanoparticles of ZnO or TiO_2. Such sunscreens are transparent, less greasy, and less smelly providing an increased aesthetic appeal.

About 40% of the solar radiation is constituted of visible radiation (from it we can protect ourselves), whereas about 60% is constituted of ultraviolet radiation responsible for acute and chronic lesions. In the first case, burnings of the cornea could occur. In the second case, cataracts, ocular degenerations (retina alterations), or tumors of the eyelids could occur.

The WHO (World Health Organization) says that about 20% of cataracts are caused by excessive exposure to ultraviolet radiation.

The recommended solar protection factors (SPF) depends upon the skin phototype, and the Fitzpatrick scale of skin phototypes developed in 1975 comprises six phototypes:

Type I Individuals with very white skin and blue or green eyes and freckles on the face, represented in northern European countries, such as the United Kingdom; always burns, never tans.

Type II Individuals with white skin, red hair, blue eyes, and freckles, represented in European Scandinavian countries; usually burns, tans with difficulty.

Type III Individuals with white skin, represented in southern and central European countries; sometimes mildly burns, gradually tans.

Type IV Individuals with morena skin, represented in Mediterranean, Asian, and Latino countries; rarely burns, tans depending on the case.

Type V Brown to dark brown, represented in East Indian, African, and native American countries; very rarely burns, tans very easily.

Type VI Very dark brown to black, represented in African countries, equatorial countries in particular; never burns, tans very easily.

FPS factors range from +50 for Type I down to 6 for type VI.

Chemical solar filters are mostly aromatic organic compounds, the most common being p-amino benzoic acid and its derivative compounds, cinnamic acid and its esters, benzimidazoles, and products derived from sulfonic acid, benzophenones, and dibenzoylmethane. Solar filters based on minerals are safer than solar filters based on chemicals which are easily skin absorbed. An alarming very recent report highlights dangers of sunscreens for children. Two French Environmental Associations, WECF and Agir pour l'Environnement, based on studies carried out in 71 (seventy-one) cosmetic products (creams, lotions, mousses, milks, and sprays) used for children and reported in 2020, found that none of the sunscreens tested were free from the substances of concern, 9 sunscreens were identified as containing a mixture of at least 10 ingredients of concern, including endocrine disruptive substances, nanoparticles, and allergens, one of these substances being the *phenoxyethanol*. Three products were found to contain nanoparticles not indicated on the label and therefore noncompliant with the cosmetics regulation.

Finally, biological filters are natural organic molecules (e.g., ascorbic acid, tocopherol, and their derived products) with antioxidant properties and able to sequestrate free radicals responsible for aging. Besides, they coadjuvate photoprotecting activity of physical and chemical filters, improve skin elasticity, and potentiate the immunological cutaneous subsystem. Every cm^2 of the body exposed to solar radiation should be covered with 2 mg of solar protection cream, which means that 36 g (the equivalent to six coffee spoons) are required for adequate body coating.

Clay minerals are widely used in sunscreen formulations due to their protective effect against UV rays and nonallergic and nontoxic properties. The sunscreen properties of clay minerals are specifically attributed to their ability to scatter and adsorb radiant energy and thus protect DNA in skin cells from UV damage. *Montmorillonite* and *hectorite* organoclays are increasingly recognized as effective sunscreen agents.

Toothpastes Some minerals are currently incorporated in toothpastes for two purposes: as agents to diminish teeth sensitivity and as abrasive or polishing agents.

Minerals, containing potassium and nontoxic anions and being highly soluble in water, well exemplified by the mineral *niter* (KNO_3), are used in toothpaste formulations good for sensitive teeth; K^+ ions act on nerve endings inside dentine inhibiting the transmission of painful stimuli (Orchardson and Gillam 2000; Wara-Aswapati et al. 2005). Such formulations due their both pharmaceutical and cosmetic character could be classified as *cosmeceuticals*. *Calcite* ($CaCO_3$) is another mineral currently incorporated in toothpaste as abrasive/polishing agent due to the following two properties: *high whiteness* and *low abrasivity* (hardness of 3 in the Mohs scale comparatively to tooth enamel hardness (5 in the Mohs scale)).

Creams, Powders, and Emulsions Creams, powders, and emulsions containing some specific minerals are applied to external parts of the body in order to embellish or modify their physical appearance or to preserve the physicochemical conditions of the skin.

Bathroom Salts and Deodorants Some minerals, such as *halite* (NaCl), *sylvite* (KCl), *epsomite* ($MgSO_4.7H_2O$), and *mirabilite* ($Na_2SO_4.10H_2O$), are used in bathroom salts due to their specific chemical composition and particularly to their high solubility in water.

Lipsticks and Lip Care Nanoparticles of different nature can be incorporated into lipstick and lip gloss in order to soften or smoothen the lips by preventing transepidermal water loss. *Pigments* exhibit a wide range of colors using *gold* (Au) or *silver* (Ag) *nanoparticles* mixed in various compositional ratios whose color can be maintained for a long period of time; *silica* nanoparticles used in lipsticks improve the homogeneous distribution of pigments, and once applied they prevent the pigments from migrating or bleeding into the fine line of the lips.

9.3.4 Properties of Clays and Clay Minerals for Cosmetic Applications

Part of the matter disclosed in the following 9.4 and 9.5 items has been extracted from the article "Clays and Human Health" produced by Carretero et al. (2006) and published in the Handbook of Clay Science edited by Bergaya F, Theng BKG, and Lagaly G of the series "Developments in Clay Science," volume 1.

Clays and clay mineral properties justify their applications in cosmetics and pharmaceuticals. Clay minerals in both cosmetic and pharmaceutical industries are often used as excipients to stabilize emulsions or suspensions and to modify the rheological behavior of these systems; they also play an important role as adsorbents and absorbents (Moraes et al. 2017).

Kaolinite and *smectites* are the main clay minerals selected for specific use in *beauty* and *spa therapy*, whereas other clays rich in *illite*, *interstratified illite/smectite*, *chlorite*, *sepiolite*, or *palygorskite* are occasionally reported on the global panorama of spa and beauty market (see the report by Elmore 2003).

Common (polymineralic) clays are also used. Besides other phyllosilicates, these clay materials contain Fe-Mn hydroxides and other associated minerals (mainly *calcite*, *dolomite*, *quartz*, and *feldspars*, but also *zeolites*, opal, and Ti oxides may occur, among many others). The presence of these associated phases should be controlled, because the final product applied to the patient should have only the required and appropriate mineral properties for their use.

One of the peculiar features of the use of clays for therapies is the wide spectrum of pathologies and aesthetic worries that are cured using them. Nonetheless, some properties of clays seem to be advisable, for most of their use is in *spa* and *aesthetic medicine* (for specific purposes the clay must be properly chosen):

1. Softness and small particle size; since the application of the clay paste, particularly as face mask, can otherwise be unpleasant.
2. Appropriate rheological properties for the formation of a viscous and consistent paste, good plastic properties for easy application, and adherence to the skin during treatment.

3. Similarity in pH to that of the skin so as to avoid irritation or other dermatological problems.
4. High adsorption capacity; clays can eliminate excess grease and toxins from the skin and hence are very effective against dermatological diseases such as boils, acne, ulcers, abscess, and seborrhea; an organic active principle can also be incorporated into the clay mineral before its application to the patient's skin for therapeutic and cosmetic purposes.
5. High cation exchange capacity (CEC), enabling an exchange of nutrients (K^+, Na^+, Ca^{2+}, Mg^{2+} or others) to take place while the clay mineral is in contact with the skin.
6. High heat retention capacity (retentiveness); as heat is also a therapeutic agent, clay paste is mostly applied hot to treat chronic rheumatic inflammations, sport traumatisms, and dermatological problems.

Montmorillonite, *saponite*, *hectorite*, *kaolinite*, *palygorskite,* and *sepiolite* are natural cationic clay minerals that fulfill many of the requirements for usage in *spa* and *beauty therapy*.

Due to their sorptive capacities, optimum rheological characteristics, and large specific surface areas, cationic clay minerals are employed in products, such as antiperspirants, skin cleansers, odor absorbers, body sprays, and deodorants. As active ingredients in cosmetics, cationic clay minerals can adsorb unwanted substances, like sebum oils, and residues generated by the sebaceous glands, toxins, greases, and odors generated by the skin or by the natural skin microbiota. As excipients cationic clay minerals are used due to their high cation exchange capacities, excellent swelling properties, hydration abilities, and suitable rheological behaviors. However, cationic clay minerals that are currently used in cosmetic formulations are often modified to improve natural properties and to impart new functionalities. New composite materials able to modify the initial hydrophilic character of clay minerals have been developed.

The rheological properties of clays and clay minerals are a subject of paramount importance in cosmetics. Every time cosmeceuticals, such as creams, are squeezed from tubes or lipsticks are applied, or yet the stability of a concentrated suspension is required, rheology is involved.

Viscosity, the resistance to flow defined by the ratio *shear stress/shear rate*, is the parameter that expresses the rheology of a system. *Shear stress* is the force per unit area being applied, and *shear rate* is the resulting velocity gradient.

The viscosity of distinctive systems can exhibit three distinctive behaviors:

1. *Newtonian flow* when viscosity maintains a constant value regardless of shear rate.
2. *Dilatant flow* when viscosity increases with shear rate increases.
3. *Pseudoplastic flow or shear thinning* when viscosity decreases with increasing shear rate.

Some systems require a specific stress to initiate the flow. This particular stress value is named *yield point*. A system characterized by both *shear thinning flow* and a *yield point* is said as having *plastic flow*. The rate of recovery of a system when stress is removed is an interesting characteristic of the system, and when a shear thinning system shows delayed viscosity recovery, it is named thixotropic. As a rule, viscosity is temperature dependent.

As a rule, natural *kaolin* and natural *bentonite*, two important clays for cosmetic applications, are clay systems that exhibit distinctive rheological behavior. *Bentonite* is frequently used as thickener additive, either as aqueous phase thickener or non-aqueous phase thickener.

Distilled water (50–60% w/w) and clay (usually *kaolin/bentonite* mixture 30–35%w/w, showing white, pink, or green color) are two fundamental and major components of facial masks, whereas propylene glycol, glycerin, and preservative are minor components.

9.4 Types of Application and Therapeutic Activity of Clay Minerals

The different types of application and therapeutic activity of clay minerals in spas and beauty therapy which have received much attention over the past 30 years are as follows: Messina and Grossi (1983), Torrescani (1990), Barbieri (1996), De Bernardi and Pedrinazzi (1996), Novelli (1996), Martín Díaz (1998), Benazzo and Todesca (1999), Lotti and Ghersetich (1999), Nappi (2001), Carretero (2002), López-Galindo and Viseras (2004), Gomes and Silva (2007), Giacomino and DeMichele (2007), Veniale et al. (2007), Rautureau et al. (2010, 2017), Gutenbrunner et al. (2010), López-Galindo et al. (2007), López-Galindo et al. (2011), and Moraes et al. (2017).

Particular types of clay, for instance, the so-called edible clays, can be used mixed and suspended in water for healing purposes (or mixed with water and other natural products to fight famine) or can be used in topical applications for healing or cosmetic purposes –*pelotherapy* – in *spas* and in *beauty therapy*, where they are mixed with mineral water, sea water, or salt lake water and then matured. Also, particular types of clay can be used, for instance, mixed with paraffin – *paramuds* – for physical and rehabilitation applications in the physiotherapy area.

In *pelotherapy* the application modalities of clay/mineral water pastes and suspensions can be used as *face masks*, *cataplasms* also called *mudpacks* or *mud-compresses*, or *mud baths*, depending on the body area to be treated, although in some spas they are also used for corporal massages. Application temperature (hot or cold) depends on the therapeutic aims. The *paramuds*, also called *parafangos* and *parapeloids*, effectively they are *peloid succedaneous* or *substitutes*, are applied only as cataplasms and always hot.

The application of *face masks* is carried out in layers 1 cm to 5 cm thick for 20–30 min. When applied hot (40–45 °C) cataplasms are covered with an impermeable material to conserve the heat. In most cases the paste is recycled from one patient to another. *Face masks* are used mainly in beauty therapy. *Cataplasms* are used in spas and in beauty therapy when the mud is applied to only a small area of the body.

Mud baths are preferentially used in spas, since the area under treatment is extensive. Application is carried out by submerging part of the body (bathing the arms, hands, or feet) or the whole body in a bowl or bathtub filled with a mixture of clay and water.

The application of warm mud is recommended particularly when *paramuds* are used in *beauty therapy* for the following therapeutic purposes:

1. To moisturize the skin, since during warm mud application the perspiration produced cannot get free since the mud paste is covered with an impermeable material; this perspiration soaks into the upper layers of the epidermis, moisturizing it from within; besides, the skin being a hyper-porous system, active substances (therapeutic or cosmetic) can easily be absorbed by the corneous layer and reach the deepest layers of the epidermis.
2. To treat compact lipodystrophies in their initial evolution when they need preventive care but cannot be treated more aggressively and before the application of cosmetics.
3. To retard the development of cellulite, given that they stimulate venous and lymphatic circulation in the application area and that they act as anti-inflammation agents.
4. For cutaneous cleaning and treating dermatological conditions such as blackheads, spots, acne, ulcers, abscess, and seborrhea; heat promotes perspiration and the flow of sebaceous secretions in a fluid state and their adsorption by the clay paste; heat also opens the pilosebaceous orifices, improving sorption of active substances.

The application of warm clay paste causes the increase of temperature on the treated area, producing vasodilatation, perspiration, and the stimulation of cardiac and respiratory frequency. These effects range from local to systemic according to the procedure conditions being used (temperature, time, body surface, etc.). As this creates a stimulatory, antiphlogistic, and analgesic action, such applications are recommended in spas, for the two following diseases:

1. Chronic rheumatic processes including degenerative osteoarthritis in any part of the body, dysendocrine arthropathies, spondilo-arthritis ankylopoietic, spondylosis, myalgias, neuralgias, etc.
2. Sequelae of osteoarthicular injuries, fractures, and dislocations, as well as disorders following vasculopathies.

We should note that hot application is contraindicated in areas of the body with circulatory problems (e.g., varicose veins) and in the acute and subacute phases of rheumatic processes, discompensated cardiopathies, tuberculosis, and renal or hepatic deficiencies. In acute pathologies (inflamed or congested areas), the application temperature must be lower than the body temperature (cold mud). Here the application produces the cooling of the area under treatment, and since the mixture is a good conductor of the heat given off by the inflammation, it acts as an anti-inflammatory agent. The mixtures can also be used cold in liquid retention problems.

Minerals, whether as active ingredients or as ideal excipients, must comply with a number of textural and compositional requirements, such as grain size, degree of mineral purity, water content, major and trace element contents, or microbial contamination. Also, they should have specific technical properties. Their safety and stability characteristics are vitally important.

According to López-Galindo et al. minerals apart of being efficient for both specific pharmaceutical and cosmetic functions, as abrasives, absorbents, adsorbents, anticaking agents, coating agents, opacifying agents, suspending agents, rheological agents, lubricants, diluents, binders, etc., in the case of clays they should also comply with some chemical (pH, stability, purity, chemical inertia), physical (texture, particle size, water content), and toxicological (atoxicity, chemical and microbiological safety). For example, in the case of clays, there are specific technical specifications for each one and its intended use. In regard to particle size for general pharmaceutical and cosmetic applications, it is less than 325 mesh (45 μm). The authors provide a review of the different pharmacopoeias' rules and regulations affecting the use of natural clays. For instance, in regard to microbiological safety, which depends on eventual contamination of microorganisms during processing, manufacture, and storage, EU and US pharmacopoeias established microbial limits (expressed in *cfu/g*) of aerobic bacteria and fungi.

Clays are usually sterilized by heating at over 160 °C for not less than 1 hour or by exposure to gamma (ϒ) radiation (Bubik 1992).

9.5 Essential and Toxic Elements in Clays for Cosmetic and Pharmaceutical Use

Clay and clay minerals used for cosmetic and medical purposes are topics of increasing scientific interest. For Roselli et al. (2015) the fundamental property that needs to be considered and maintained in any material used for pharmaceutical and cosmetic purposes is to have low or null toxicity.

Clay and clay minerals due to their high specific surface area and to the electrically charged sites on particle surfaces, in numbers much more negative than positive, can fix or adsorb, as a rule in a reversible way, from the ecosystems where they coexist, trace elements in particularly metals, and within them are those traditionally considered as toxic (As, Sb, Cd, Co, Ni, Zn, Hg, and Ba) and other less toxic elements (Li, Rb, Cr, Mo, V, and Rare Earth Elements or REE), all of them being natural constituents of both Earth's crust and biological systems. Rarely the elements referred to are strongly bound constituents in clay mineral structures, hence showing low or null mobility.

The potentially toxic elements existing in both drugs and cosmetics sometimes are not present in both clay and clay minerals, but elsewhere, in certain components

Table 9.1 Chemical limitations for heavy metals (total content) and for As and Pb

Chemical limitations	Kaolinite EP7th USP32	Talc EP7th USP32	Bentonite EP7th USP32	Sepiolite EP7th USP32	Palygorskite USP32
Al (%)	–	≤2	–	–	–
Ca (%)	≤0.025	≤0.9	–	–	–
Fe (%)	–	≤0.25	–	–	–
Mg (%)	–	17–19.5	–	–	–
As (ppm)	–	–	≤5	–	–
Pb (ppm)	≤10	≤10	≤40	–	–
H.met (ppm)	≤50	–	≤50	–	–
Chloride (%)	≤0.025	–	–	–	–
Sulfate (%)	≤0.1	–	–	–	–
pH	–	7–9	9.5–10.5	–	7–9.5

of the formulations. Since clays and clay minerals are used for treatment of various diseases, it is important to avoid possible intoxications via ingestion and dermal absorption of those potentially toxic elements present in the clays. Thus, it is necessary to determine the concentration of toxic or potentially dangerous elements within the main components of formulation matrices.

Roselli et al. (2015) have investigated using adequate analytical means 15 clay samples purchased in local stores for pharmaceutical and cosmetic uses. Energy-dispersive polarized X-ray fluorescence (EDPXRF), a sensitive, quantitative, multi-elemental, and nondestructive technique, was used by the authors. X-ray powder diffraction (XRPD) was used too to identify clay and non-clay minerals.

Si, Al, Ca, Mg, Na, K, Fe, Ti, and Mn are the normal and safe metals present in clay minerals, and any other metals are not normal, the reason why their identification and quantification it is mandatory.

The European Pharmacopeia (2011) and US Pharmacopeia (USP 32-NF27, 2009) report chemical limitations relative to heavy metal total content and to As and Pb contents (see Table 9.1).

9.6 Guidelines for Elemental Mineral Impurity Allowance in Pharmaceuticals and Cosmetics

Relative to pharmaceutical products, the ICH guideline Q3D on Elemental Impurities (EMA/CHMP/ICH 353369/2013) shows in Table 9.2 the maxima PDE values (permitted daily exposure, i.e., the maximum acceptable intake of elemental impurities per day in pharmaceuticals, drug products, drugs, and excipients) for oral, parenteral, and inhalation exposures to Ba-, Sb-, As-, Cd-, Cr-, Cu-, Co-, Au-, Pb-, Li-, Hg-, Mo-, Ni-, Pd-, Pt-, Se-, Ag-, Tl-, Sn-, and V-bearing compounds.

Table 9.2 Permitted daily exposures for elemental impurities in pharmaceutical products

Element	**Class**	**Oral PDE** (μg/day)	**Parenteral PDE** (μg/day)	**Inhalation PDE** (μg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11,000	1100	3

Other routes of administration such as dermal absorption exposure, relevant in some therapeutic and cosmetic pharmaceuticals, had been not considered.

The European Medicines Agency publishes scientific guidelines that are harmonized between Europe, Japan, and the USA by the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use.

9.7 Cosmetic Microbiology and Antimicrobial Protection

The International Standard ISO930 (2012) defines a series of steps to be taken when assessing the overall antimicrobial protection of a cosmetic product, protection that can come from the following sources: chemical preservation, inherent characteristics of the formulation, package design, and manufacturing process.

The European Commission (EC) has an early warning system for safety management called the Rapid Alert System (RAPEX).

Neza and Centini (2016) investigated the RAPEX database of this system during the period January 2008 until week 26 of 2014, in order to get microbiological information about dangerous cosmetic products sold in EU markets, and investigated too cosmetic products containing high concentrations of preservatives (Song et al. 2013).

Dangerous cosmetic products pose a risk to the consumers due to the presence of certain substances which are banned or the use of which is restricted in these products under cosmetic legislation. Cosmetic products are recognized to be substrates for the survival and development of a large variety of microorganisms, since they possess some of the nutrients that facilitate growth such as water, lipids, polysaccharides, alcohol, proteins, amino acids, glycosides, peptides, and vitamins (Herrera 2004).

The presence of pathogenic microorganisms in cosmetic products can pose a health risk for consumers. The use of preservatives, good manufacturing practices, and quality control programs has improved cosmetic quality, but several studies have reported cases of contaminated cosmetic products (Lundov and Zachariae 2008; Wong et al. 2000; Hugbo et al. 2003).

Research studies have shown several cases of infection caused by contaminated cosmetics (Ashour et al. 1989; Mpuchane et al. 2010).

According to SCCP's (Scientific Committee on Consumer Products) "Notes of Guidance," cosmetic products are divided into two different categories:

1. Products specifically intended for children under 3 years or to be used in the eye area and on mucous membranes
2. Other products

According to the Guidelines on Microbial Quality Management (1997), the products intended for use on babies and the eye area (category 1) should have not more than 102 Cfu/g or mL of aerobic mesophilic microorganism (other products not more than 103 Cfu/g or mL). *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, or *Escherichia coli* must not be detectable in 0.5 g or 0.1 mL of product category 1 and in 0.1 g or 0.1 mL of product category 2.

The studies carried out by Neza and Centini (2016) using the RAPEX database had shown that the European consumers are exposed to microbiologically contaminated and overpreserved cosmetic products. The authors mention that most frequently found microorganisms in cosmetics are *P. aeruginosa*, *K. oxytoca*, *B. cepacia*, *S. aureus*, *E. coli*, *C. albicans*, *E. gergoviae*, and *S. marcescens*, but also other bacteria, fungi, and yeasts.

To prevent the microbial contamination of cosmetic products, chemical substances with known antimicrobial properties are used. The EU regulation 1223/2009 provides a list of allowed preservatives in cosmetic products with maximum concentrations in ready-for-use preparation. Preservatives are known as one of the most relevant allergens found in cosmetic products (Timm-Knudson et al. 2006; Maier et al. 2009).

Also, the studies carried out by Neza and Centini (2016) found out cosmetic products contain high concentrations of preservatives, and formaldehyde was one of them. This chemical used in cosmetics as a preservative for its antimicrobial properties, and that had been classified as a carcinogen, as well as other chemicals used as preservatives (methyldibromo glutaronitrile, methylisothiazolinone, triclosan, and benzalkonium chloride, some already banned in EU countries), may pose health risks to consumers.

References

Aguzzi C, Cerezo P, Viseras C, Caramella C (2007) Use of clays as drug delivery systems: possibilities and limitations. Appl Clay Sci 36:22–36

Aguzzi C, Sandri G, Cerezo P, Carazo E, Viseras C (2016) Health and medical applications of tubular clay minerals. Developments in clay science, vol 7. Elsevier, Amsterdam, pp 708–725

Alam H, Zheng C, Jaskille A, Querol R, Koustova K, Inocencio R, Conran R, Seufert A, Ariaban N, Toruno K, Rhee P (2004) Application of a zeolite hemostatic agent achieves 100% survival in a lethal model of complex groin injury in swine. J Trauma Inj Crit Care 56:974–983

Ashour E, Abdelaziz AA, Hefni H, El-Tayeb M (1989) Microbial contamination of cosmetics and personal care items in Egypt: body lotion and talcum powders. J Clin Pharm Ther 14:207–212

Awad ME, López-Galindo A, Setti M, El-Rahmany MM, Viseras C (2017) Kaolinite in pharmaceutics and biomedicine. Int J Pharm 533:34–48

Baker SE, Sawvel AM, Zheng N, Stucky GD (2007) Controlling bioprocesses with inorganic surfaces: layered clay hemostatic agents. Chem Mater 19:4390–4392

Barbieri P (1996) Validitá terapêutica dei fanghi delle Terme di Salice. In: Veniale F (ed) Atti Convegno “Argille Curative”. Salice Terme/PV, Gruppo Italiano AIPEA, pp 13–15

Bedoux G, Roig B, Thomas O, Dupont V, Le Bot B (2011) Occurrence and toxicity of antimicrobial triclosan and by-products in the environment. Environ Sci Pollut Res. Published online 05 November 2011, Springer. https://doi.org/10.1007/s11356-011-0632-z

Benazzo F, Todesca A (1999) Terapia Termale nella riabilitazione dei traumi delle sportivo. In: Abstracts Simposio “Argille per fanghi peloidi termali e per trattamenti dermatologici e cosmetici”. Montecatini Terme. Gruppo Italiano AIPEA

Bertolani M, Loschi-Ghittoni AG (1996) I fanghi argillosi usati nelle terapie delle terma dells Salvarola (Sassuolo-Modena). Atti Convegno “Argille Curative”, Veniale F (editor), Sálice Terme/PV, 129-137, Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física (AMIITTE) and Gruppo Italiano AIPEA (Association Internationale pour L’Étude des Argiles)

Bettero A, Dall’Aglio C, Semenzato A, Tollardo A, Lalli A (1994a) Richerche bio-termologiche applicate al termalismo. Cosmesi Derm 48:23–32

Bettero A, Austria R, Dall’Aglio C, D’Alpaos M, Tollardo A, Semenzato A, Lalli A (1994b) Controllo e modulazione della funzione epidérmica di permeabilitá agli elementi termali specifici rilasciati da un fango maturo. Cosmesi Derm 50:7–14

Bonferoni MC, Cerri G, De’Gennaro M, Juliano C, Caramella C (2007) Zn^{2+}exchanged clinoptilolite-rich rock as active carrier for antibiotics in anti-acne topical therapy: in-vitro characterization and preliminary formulation studies. Appl Clay Sci 36:95–102

Braun DB (1994) Over-the-counter pharmaceutical formulations. Noyes Publications, Park Ridge, 459pp

Browne JE, Feldkamp JR, White JL, Hem SL (1980) Characterization and adsorptive properties of pharmaceutical grade clays. J Pharm Sci 69:816–823

Bubik JS (1992) Preparation of sterile talc for treatment of pleural effusion. Am J Hosp Phar 49:562–563

Bund B (2017) Technically avoidable heavy metal contents in cosmetic products. J Consumer Protection Food Safety 12(1):51–53

Butler H (2000) Cosmetics through the ages. In: Poucher’s perfums, cosmetics and soaps, 10th edn. Dordrecht, Kluwer Academic Press, pp 13–64

Cara S, Carcangiu G, Ligas P, Padalino G, Palomba M, Tamanini M, Uras I (1996) Possibilita’ di Impiego delle bentoniti sarde nel campo delle argille sanitarie. Atti Convegno “Argille Curative”, Sálice Terme, Veniale F (editor), 103-117, Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física (AMIITTE) and Gruppo Italiano AIPEA (Association Internationale pour L’Étude des Argiles)

Carazo E, Borrego-Sánchez A, García-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C, Viseras C (2018) Advanced inorganic nanosystems for skin drug delivery. The Chemical Record, pp 891–899).. https://doi.org/10.1002/tcr.201700061

Carretero MI (2002) Clay minerals and their beneficial effects upon human health: a review. Appl Clay Sci 21:155–163

Carretero MI, Pozo M (2007) Mineralogía aplicada: salud y medio ambiente. Thomson, Madrid, 464pp

Carretero MI, Pozo M (2009) Clay and non-clay minerals in the pharmaceutical industry, Part I: excipients and medical applications. Appl Clay Sci 46:73–80

Carretero MI, Pozo M (2010) Clay and non-clay minerals in the pharmaceutical and cosmetic industries, Part II: Active ingredients. Appl Clay Sci 47:171–181

Carretero MI, Gomes CSF, Tateo F (2006) Clays and human health. In: Bergaya F et al (eds) Handbook of clay science. Developments in Clay Science, Elsevier, Amsterdam, pp 717–741

Carretero MI, Lagaly G, Schwalter M (2007) Clays and health-clays in pharmacy, cosmetics, pelotherapy, and environmental protection. Appl Clay Sci 36(1–3):1–200

Cerezo P, Iborra CV, López-Galindo A, Ferrari F, Caramella C (2001) Use of water uptake and capillary suction time measures for the evaluation of the anti-diarrhoeic properties of fibrous clays. Appl Clay Sci 20:81–86

Cerri G, De'Gennaro M, Bonferoni MC, Caramella C (2004) Zeolites in biomedical application: Zn-exchanged clinoptilolite-rich rock as active carrier for antibiotics in anti-acne topical therapy. Appl Clay Sci 27:141–150

Cerri G, De'Gennaro M, Bonferoni MC, Caramella C, Juliano C (2006) Zn exchanged clinoptilolite rich rock as carrierfor erythromycin in antiacne therapy: an in vitro evaluation. In: Book of Abstracts of the 7th International Conference on the Occurrence, Properties, and Utilization of Natural Zeolites Socorro, New Mexico, USA

Changbing Y, Jian J, Shengying X, Qinghua Xu (2008) Method for producing attapulgite clay/herb composite toothpaste. Patent number: CN 101229111

Chen L, Lian G, Han L (2010) Modeling transdermal permeation. Part I: Predicting skin permeability of both hydrophobic and hydrophilic solutes AICHE J:561136–561146. https://doi.org/10.1002/aic.12048

Dawson JI, Oreffo ROC (2013) Clay: new opportunities for tissue regeneration and biomaterial design. AdvMater 25:4069–4086

De Bernardi M, Pedrinazzi GM (1996) Azioni biologiche dei fanghi termali. Atti Convegno "Argille Curative", Sálice Terme/PV, Veniale F (editor), 17-24. Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física (AMIITTE) and Gruppo Italiano AIPEA (Association Internationale pour L'Étude des Argiles)

De Sousa LA, Figueiras A, Veiga F, de Freitas RM, Nunes C, Silva D (2013) The systems containing clays and clay minerals from modified drug release: a review. Colloids Surf B Biointerfaces 103:642–651

Del Hoyo C (2007) Layered double hydroxides and human health: an overview. Appl Clay Sci 36:103–121

Droy-Lefaix MT, Tateo F (2006) Clays and clay minerals as drugs. In: Bergaya F, Theng BKG, Lagaly G (eds) Handbook of Clay Science. Elsevier, Amsterdam, pp 743–752

Elmore AR (2003) Final report on the safety assessment of aluminum, silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite "Fuller's earth", hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. Int J Toxicology 22(Suppl. 1):37–102

European PharmacopoeiaPharmacopoeias, 7th ed. (2011) Strasbourg, France: European Pharmacopoeia Convention

Fang J (1988) Powder pharmaceuticals containing attapulgite for treatment of chronic ulcer in the lower extremities. Patent number: CN 86105579

Ferrand T, Yvon J (1991) Thermal properties of clay pastes for pelotherapy. Appl Clay Sci 6:21–38

Gaharwar AK, Avery RK, Assmann A, Paul A, McKinley GH, Khademhosseini A, Olsen BD (2014) Shear-thinning nanocomposite hydrogels for the treatment of hemorrhage. ACS Nano 8:9833–9842. https://doi.org/10.1021/nn503719n

Gálan E, Singer A (2011) Developments in palygorskite and sepiolite research: a new outlook on these nanomaterials. Developments in Clay Science, volume 3, Gálan E and Singer A (eds)

Gálan E, Liso MJ, Forteza M (1985) Minerales utilizados en la indústria farmacêutica. Bolde la Sociedad Española de Mineralogia 8:369–378

Gamiz E, Linares J, Delgado R (1992) Assessment of two Spanish bentonites for pharmaceutical uses. Appl Clay Sci 6(5–6):359–368

Ghadiri M, Chrzanowski W, Rohanizadeh R (2014) Biomedical applications of cationic clay minerals. The Royal Society of Chemistry

Giacomino MI, DeMichele DF (2007) Is mud an anti-inflammatory? An. Med Interna 24:352–353

Glick JB, Kaur RR, Siegel D (2013) Achieving hemostasis in dermatology-Part II: Topical hemostatic agentes. Indian Dermatol. Online J 4(3):172–176

Gomes CSF, Silva JBP (2007) Clay minerals and non-clay minerals in Medical Geology. Appl Clay Sci 36:4–21

Gomes CSF, Gomes JH, Tacão M, Henriques I, Silva EF (2019) Bactericidal clay to be used as topical ointment in skin infections. III Simposio Internacional de Termalismo y Calidad de Vida (SCTV-2019) / III International Symposium on Thermalism and Quality of Life. Campus da Auga, Ourense, Spain

Gomes C, Silva AC, Marques AC, Sousa Lobo JM, Amaral MH (2020a) Biotechnology applied to cosmetics and aesthetic medicines. Cosmetics 7:33. https://doi.org/10.3390/cosmetics7020033

Gomes CSF, Gomes JH, Silva EAF (2020b) Bacteriostatic and bactericidal clays: an overview. Environ Geochem Health. https://doi.org/10.1007/s10653-020-00628-w

Gutenbrunner C, Bender T, Cantista P, Karagulle Z (2010) A proposal for a worldwide definition of Health Resort Medicine, Balneology, Medical Hydrology and Climatology. Int J Biometereol:1–13

Hári J, Polyák P, Mester D, Micusik M, Omastová M, Kállay M, Pukánsky B (2016) Adsorption of an active molecule on the surface of halloysite for controlled release application: interaction, orientation, consequences. Appl Clay Sci 132–133:167–174

Hermosin MC, Cornejo J, White JL, Hem S (1981) Sepiolite, a potential excipient for drugs subject to oxidative degradation. J Pharm Sci 70(2):189–192

Hernández D, Lazo L, Valdés L, Ménorval LC, Rozynek Z, Rivera A (2018) Synthetic clay mineral as nanocarrier of sulfamethoxazole and trimethoprim. Appl Clay Sci 161:395–403

Hernández AC, Awad ME, Melendez W, González G, Lopez-Galindo A, Sánchez-Espejo R, Garcia-Villen F, Viseras C (2019) Colloidal and thermal behaviours of some Venezuelan kaolin pastes for therapeutic applications. Fortschr Mineral 9

Herrera GA (2004) Microbiological analysis of cosmetics. Methods Mol Biol 268:293–295

Hu Y, Wang H, Tong C (2006) Attapulgite solid and liquid preparation for cure digestive tract disease. Patent number: CN 1739575

Hugbo PB, Onyekweli AO, Igwe I (2003) Microbial contamination and preservative capacity of some brands of cosmetic creams. Trop J Pharm Res 2:229–234

Iannuccelli V, Maretti E, Bellini A, Malferrari D, Ori G, Montorsi M, Leo E (2018) Organo-modified bentonite for gentamicin topical application: interlayer structure and in vivo skin permeation. Appl Clay Sci 158:158–168

Khurana S, Kaur S, Kaur H, Khurana RK (2015) Multifaceted role of clay minerals in pharmaceuticals. Future Sci OA 1(3):FSO6

Kumar V, Chakraborty A, Kural MR, Roy P (2009) Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reprod Toxicol 27(2):177–185

Lefort D, Deloncle R, Dubois P (2007) Les minéraux en pharmacie. Géosciences 5:6–19

López-Galindo A, Viseras C (1996) Usos farmacêuticos de arcillas especiales (sepiolita y paligorskita). Atti Convegno “Argille Curative”, Sálice Terme/PV, Veniale F (editor), 45-53, Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física (AMIITTE) and Gruppo Italiano AIPEA (Association Internationale pour L'Étude des Argiles)

López-Galindo A, Viseras C (2004) Pharmaceutical and cosmetic applications of clays. In: Wypych F, Satyanarayana KG (eds) Clay surfaces: fundamentals and applications. Elsevier Ltd, pp 267–289

López-Galindo A, Viseras C, Aguzzi C, Cerezo P (2011) Pharmaceutical and cosmetic uses of fibrous clays. Developments in clay science, 3, Elsevier B.V., Doi: https://doi.org/10.1016/B978-0-444-53607-5.00013-X

Lotti T, Ghersetich I (1999) Peloidi: trattamento dermato-cosmetologico termale emergente. In: Abstracts Simposio "Argille per fanghi peloidi termali e per trattamenti dermatologici e cosmetici". Montecatini Terme. Gruppo Italiano AIPEA

Lundov MD, Zachariae C (2008) Recalls of microbiologically contaminated cosmetic in EU from 2005 to May 2008. Int J Cosmet Sci 6:471–474

Madkour AA, Madini EMH, El-Azzonni OEZ, Amer MA, El-Walidi TM, Abbass T (1993) Smectite in acute diarrhea of children: A double-blind placebo controlled clinical trial. J Pediatric Gasteroenterol Nutr 17(2):176–181

Maier LE, Lampel HP, Bhutani T, Jacob SE (2009) Hand dermatitis: a focus on allergic contact dermatitis to biocides. Dermatol Clin 27:251–264

Martín Díaz L (1998) Arcillas, peloides, parafangos en medicina estética. Tesis de Máster Universitario de Medicina Estética, Uiversidad Islas Baleares, 45pp

Mattioli M, Giardini L, Roselli C, Desideri D (2016) Mineralogical characterization of commercial clays used in cosmetics and possible risks for health. Appl Clay Sci 119:449–454

Messina B, Grossi F (1983) Elementi di Idrologia Medica. Universo Ed, Roma

Mitragotri S (2003) Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. J Control Release 86:69–92. https://doi.org/10.1016/S0168-3659(02)00321-8

Mitragotri S, Anissimov YG, Bunge AL, Frasch HF, Guy RH, Hadgraft J, Kasting GB, Lane ME, Roberts MS (2011) Mathematical models of skin permeability: an overview. Int J Pharm 418:115–129. https://doi.org/10.1016/j.ijpharm.2011.02.023

Moraes JDD, Bertolino SRA, Cuffini SL, Ducart DF, Bretzke PE, Leonardi GR (2017) Clay minerals: properties and applications to dermocosmetic products and perspectives of natural raw materials for therapeutic purposes – a review. Int J Pharm 534:213–219

Mpuchane SF, Ekosse GE, Gashe BA, Morobe I, Coetzee SH (2010) Microbiological contamination of Southern African medicinal and cosmetic clays. Int J Environ Health 20(1):27–41

Nappi G (2001) Medicine and thermal clinic. Edizioni Selecta Medica, Pavia, Italia

Naumenko EA, Guryanov ID, Yendluri R, Lvov YM, Fakhrullin RF (2016) Clay nanotube–biopolymer composite scaffolds for tissue engineering. Nanoscale 8:7257–7271

Neza E, Centini M (2016) Microbiologically contaminated and over-preserved cosmetic products according Rapex 2008-2014. Cosmetics 3(3). https://doi.org/10.3390/cosmetics3010003

Novelli G (1996) Applicazioni medicali e igieniche delle bentoniti. Atti Convegno "Argille Curative", Sálice Terme/PV, Veniale F (editor), 25-43, Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física (AMIITTE) and Gruppo Italiano AIPEA (Association Internationale pour L'Étude des Argiles)

Orchardson R, Gillam DG (2000) The efficacy of potassium salts as agents for treating dentin hypersensitivity. J Orofac Pain Winter 14(1):9–19

Oya A, Banse T, Ohashi F (1992) Antimicrobial and antifungal agent derived from clay minerals. Appl Clay Sci 6, 301-310 and 311-318

Pandey A, Höffer R, Larroche C, Taherzadeh M, Nampoothiri M (2015) Industrial biorefineries and white biotechnology, 1st edn. Elsevier Science, New York, pp 608–640

Pereira RF, Bártolo PJ (2016) Traditional therapies for skin wound healing. AdvWound Care 5(5):208–229

Pierchala MK, Makaremi M, Tan HL, Pushpamalar J, Muniyandy S, Solouk A, Lee SM, Pasbakhsh P (2018) Nanotubes in nanofibers: antibacterial multilayered polylactic acid/halloysite/gentamicin membranes for bone regeneration application. Appl Clay Sci 160:95–105

Polefka TG, Bianchini RJ, Shapiro S (2012a) Interaction of mineral salts with the skin: A literature survey. Int J Cosmetic Science 34:416–423

Polefka TG, Meyer TA, Agin PP, Bian RJ (2012b) Effect of solar radiation on the skin. J Cosmetic Dermatol 11(2):134–143

Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W, Wurm EMT, Young C, Robertson TA, Soyer HP, Roberts MS (2011) Nanoparticles and microparticles for skin drug delivery. Adv Drug Deliv 63(6):470–491

Ramasamy T, Ruttala HB, Gupta B, Poudel BK, Choi H-G, Yong CS, Kim JO (2017) Smart chemistry-based nanosized drug delivery systems for systemic applications: a comprehensive review. J Control Release 258:226–253

Rautureau M, Liewig N, Gomes CSF, Katouzian-Safadi M (2010) Argiles et Santé: Propriétés et Thérapies. Lavoisier (editeur), Paris

Rautureau M, Gomes CSF, Liewig N, Katouzian-Safadi M (2017) Clays and health: properties and therapeutic uses. Springer, Cham. ISBN: 978-3-319-42883-3

Robertson RHS (1996) Cadavers, Choleras and clays. Br Min Soc Bull 113:3–7

Rodrigues LAS, Figueiras A, Veiga F, Freitas RM, Nunes LCC, Filho ECS, Leite CMS (2013) The systems containing clays and clay minerals from modified drug release: a review. Colloids Surf. B Biointerfaces 103:642–651

Roselli C, Desideri D, Cantaluppi C, Mattioli M, Fasson A, Meli MA (2015) Essential and toxic elements in clays for pharmaceutical and cosmetic uses. J Toxicol Environ Health Part A 78:1–9

Saha K, Butola BS, Joshi M (2014) Synthesis and characterization of chlorhexidine acetate drug–montmorillonite intercalates for antibacterial applications. Appl Clay Sci 101:477–483

Sanchez-Martin MY, Sanchez-Camazano M, Sayalero ML, Dominguez-Gil A (1988) Physicochemical study of the interaction of montmorillonite with hydrazine hydrochloride, a vascular drug. Appl Clay Sci 3:53–62

Sandri G, Bonferoni MC, Rossi S, Ferrari F, Aguzzi C, Viseras C, Caramella C (2016) Clay minerals for tissue regeneration, repair, and engineering. In: Ågren MS (Ed.). Wound healing biomaterial. Elsevier, pp 385–402

Sandri G, Faccendini A, Longo M, Ruggeri M, Rossi S, Bonferoni MC, Miele D, Prina-Mello A, Aguzzi C, Viseras C, Ferrari F (2020) Halloysite-and montmorillonite-loaded scaffolds as enhancers of chronic wound healing. Pharmaceuticals, MDPI 12:179. https://doi.org/10.3390/pharmaceutics12020179

Savarit R (1987) Les boues thermals d'intérét thérapeutique: definition et classification actualisées. Press Therm Climat 1:14–18

Scientific Committee on Consumer Products: The SCCP's Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006

Sironmandi TA (2015) Comparison of nanocarriers for gene delivery and nanosensing using montmorillonite, silver nanoparticles and multiwalled carbon nanotubes. Appl Clay Sci 103:55–61

Smith AH, Laird C, Porter K, Bloch M (2013) Haemostatic dressings in prehospital care. Emerg Med Journal 30:784–789

Song JB, Ahn IY, Cho KT, Kim YJ, Kim HS, Lee BM (2013) Development and application of risk management system for consumer products in compliance with global harmonization. J Toxicol Environ Health B Crit Rev 16:1–16

Sorg H, Tilkorn DJ, Hager S, Hanser J, Mirastschijski U (2017) Skin wound healing: an update on the current knowledge and concepts. Eur Surg Res 58:81–94

Timm-Knudson VL, Johnson JS, Ortiz KJ, Yiannias JA (2006) Allergic contact dermatitis to preservatives. Dermatol Nurs 18:130–136

Toedt J, Koza D, Cleef-Toedt K (2005) Chemical composition of everyday products. Greenwood Press, Westport

Torrescani C (1990) Utilizzo del fango termale sulfúreo nel tratamento della cute seborreica. Cosmesi Dermatologica 30:59–71

U.S. PharmacopoeiaPharmacopoeias 32-NF 27 (2009) Rockville, MD: U.S. Pharmacopoeial Convention

Ueda H, Hamayoshi M (1992) Sepiolite as a deodorant material: an ESR study of its properties. J Mater Sci 27:4997–5002

Uhlen S, Toursel F, Gottrand F (2004) Traitement des diarrheas aiges: Les habitudes de prescription des pédiatres libéraux. Arch Pédiatr 11:902–907

Ullah H, Noreen S, Fozia, Rehman A, Waseen A, Zubair S, Adnan M, Ahmad I (2017) Comparative study of heavy metals content in cosmetic products of different countries marketed in Khyber Pakhtunkhwa, Pakistan. Arab J Chem 10(1):10–18. https://doi.org/10.1016/j.arabjc.2013.09.021

Veldhoen N, Skirrow RC, Osachoff H, Wigmore H, Clapson DJ, Gunderson MP, et al. (2006) The bactericidal agent triclosan modulates thyroid hormone-associated gene expression and disrupts Akram Ashames et al /J Pharm Sci Res 11(1), 80(3):217–27

Veniale F (1992) Clay science: facts and perspectives. In: Proceedings of the mediterranean clay Meeting, Lipari, 27–30 September 1992, Mineralogic et Petrographica Acta. XXXV-A:13–44

Veniale F (1996) Argille Curative: Anteffati, Fatti e Misfatti. Atti Convegno «Argille Curative», Sálice Terme/PV, Veniale F (editor), 1-11, Associazione Medica Italiana di Idroclimatologia, Talassologia e Terapia Física (AMIITTE) and Gruppo Italiano AIPEA (Association Internationale pour L'Étude des Argiles)

Veniale F (1997) Applicazioni e utilizzazioni medico-sanitarie di materiali argilosi (naturali e modificati). In: Morandi N, Dondi M (eds) Argille e Materiali delle Argille. Guida a lla Definizione di Caratteristiche e Proprietá per gli Usi Industriali. Corso di Formazione, Gruppo Italiano AIPEA, Rimini, Italy, pp 205–239

Veniale F, Bettero A, Jobstraibizer P, Setti M (2007) Thermal muds: perspectives of innovations. Appl Clay Sci 36:141–147

Viseras C, López-Galindo A (1999) Pharmaceutical applications of some Spanish clays (sepiolite, palygorskite, bentonite): some preformulation studies. Appl Clay Sci 14:69–82

Viseras C, López-Galindo A (2000) Characteristics of pharmaceutical grade phyllosilicate powders. Pharm Dev Technol 5(1):47–52

Viseras C, Ferrari F, Yebra A, Rossi S, Caramella C, López-Galindo A (2001) Disintegrant efficiency of special phyllosilicates: smectite, palygorskite, sepiolite. STP Pharm Sci 11(2):137–143

Viseras C, Aguzzi C, Cerezo P, Lopez-Galindo A (2007) Uses of clay minerals in semisolid health care and therapeutic products. Appl Clay Sci 36:37–50

Viseras C, Cerezo P, Sanchez R, Salcedo I, Aguzzi C (2010) Current challenges in clay minerals for drug delivery. Appl Clay Sci 48:291–295

Viseras C, Aguzzi C, Cerezo P (2015) Medical and health applications of natural mineral nanotubes. In: Natural mineral nanotubes: properties and applications. Apple Academic Press, Oakville/Waretown, pp 437–448

Viseras C, Carazo E, Borrego-Sánchez A, Garcia-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C (2019) Clay minerals in skin drug delivery. Clay Clay Miner. https://doi.org/10.1007/s42860-018-0003-7

Walters KA, Roberts MS (2019) Chapter 2: Skin morphology, development and physiology. In: HAE B, Roberts MS, Leite-Silva VR, Walters KA (eds) Cosmetic formulation: principles and practice. CRC Press, Taylor & Francis Group

Wang C-F, Tian Y (2015) Reproductive endocrine-disrupting effects of triclosan: Population exposure, present evidence and potential mechanisms. Environ Pollut 206:195–201

Wang TF, Kasting GB, Nitsche JM (2007) A multiphase microscopic diffusion model for stratum corneum permeability. II. Estimation of physicochemical parameters, and application to a large permeability database. J Pharm Sci 96:3024–3051. https://doi.org/10.1002/jps.20883

Wara-Aswapati N, Krongnawakul D, Jiraviboon D, Yanon S, Karimbux N, Pitiphat W (2005) The effect of a new toothpaste containing potassium nitrate and triclosan on gingival health, plaque formation and dentine hypersensitivity. J Clin Periodontol 32(1):53–58

White JL, Hem SL (1983) Pharmaceutical aspects of clay-organic interaction. Ind Eng Chem Prod Rev Dev 22:665–671

Williams LB, Metge DW, Eberl DD, Harvey RW, Turner AG, Prapaipong P, Poret-Peterson AT (2011) What makes a natural clay antibacterial? Environ Sci Technol 45:3768–3773

Wong S, Street D, Delgado SI, Klontz KC (2000) Recalls of foods and cosmetics due to microbial contamination reported to the U.S. Food and Drug Administration. J Food Prot 63:1113–1116

Yu WH, Li N, Tong DS, Zhou CH, Lin CXC, Xu CY (2013) Adsorption of proteins and nucleic acids on clay minerals and their interactions: a review. Appl Clay Sci 80-81:443–452

Yvon J, Ferrand T (1996) Preparation ex-situ de peloides: Proprietés thermiques, mecaniques et d'echange. Atti Convegno « Argille Curative », Sálice Terme/PV, Veniale F (editor), 67–78

Zhang J, Feng D, Yin S, Gao F, Li M (2004) Pharmaceutical composition for treating diarrhea containing superfine attapulgite and antibacterial. Patent number: CN 1476873

Zhang M, Li S, Zhang W, Xu D (2009) Application of attapulgite to prepare the medical preparations for treating chronic renal failure. Patent number: CN 101347453

Chapter 10
Nanominerals and Nanomaterials Utilized in Pharmacy and Therapeutics

Celso S. F. Gomes, Delfim F. G. Santos, and Maria Helena R. Amaral

Abstract The chapter is initiated with basic data, particularly with the concepts of nanoparticle, nanomineral and nanomaterial. Nanostrutured materials based on nanoparticles constitute fundamental components of the human body. In the natural environment, the nanoparticles of origin both geogenic and anthropogenic are everywhere, in the soil, in the air, and in the water, and when they interact with the human body, they can be incorporated, and in some circumstances, they can be toxic. Nanominerals and nanomaterials are prepared to be used, for example, in pharmacy, cosmetics, and medicine. Nanoparticles are potential nanocarriers for direct cell/tissue delivery of therapeutic or diagnostic compounds. Clay and clay minerals are good examples of nanomaterials and nanominerals. The so-called organoclays are biocomposites very important in various technologies such as biosensors, regenerative medicine, and tissue engineering. Within the nanominerals, which are the devices or "machines" small enough to "travel" inside the human body to provide health benefits, some which are important in regenerative medicine/tissue engineering deserve particular reference and description. Bioactive ceramics and glasses to make prostheses can be implanted to replace and repair diseased or damaged body parts. The chapter ends with the report and discussion of both toxicity and regulation of nanominerals and nanomaterials.

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit "GeoBioTec",
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

D. F. G. Santos · M. H. R. Amaral
Faculty of Pharmacy, University of Porto, Porto, Portugal
e-mail: dsantos@ff.up.pt; hamaral@ff.up.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_10

10.1 Basic Data and Concepts on Nanoparticle, Nanomineral, and Nanomaterial

By definition *nanominerals* and *nanomaterials* are *minerals s.s.* and manufactured products that can even be derived from *minerals s.s.*, whose constituent particles have nanometric dimensions expressed in nanometers, *nanometer* (nm) being a subunit of the meter, such that 1 nm = 10^{-9} m. A nanometer is a unit of the International System of Units or Système International d' Unites (SI). It is current to say that the dimension of 1 nm is equivalent to the value of the quotient *tennis ball diameter/Earth diameter*.

The very recent review on *nanoparticles* (NPs) and *nanomaterials* (NMs) or nanostructured materials (NSMs) produced by Jeevanandam et al. (2018) published in the Beilstein Journal of Nanotechnology emphasizes the paramount importance of a research area that has gained prominent technological importance too. The authors show the results of the attempt or major challenge to develop a single international definition for NMs.

Today, there are several pieces of legislation both in European Union (EU) and the USA with specific references to NMs.

Different organizations have different definition for NMs, situation exemplified as follows:

1. For Environmental Protection Agency (EPA), "NMs can exhibit unique properties dissimilar than the equivalent chemical compound in a larger dimension," i.e., size is a determining factor (UN 2012).
2. For US Food and drug Administration (USFDA), "NMs is a material that has at least one dimension in the range of approximately 1 to 100nm and exhibit dimension-dependent phenomena" (FDA 2011).
3. For International Organization for Standardization (ISO), "NMs is a material with any external nanoscale dimension or having internal nanoscale surface structure" (ISO/TS 2010).
4. For British Standards Institution, "NMs is any internal or external structures on the nanoscale dimension, 1 to 1000nm size range" (PAS 2011).

Jeevanandam et al. (2018) have classified NMs into 4 (four) categories and gave examples in all categories:

1. Carbon-based nanomaterials
2. Inorganic-based nanomaterials
3. Organic-based nanomaterials
4. Composite-based nanomaterials

Also, the authors have proposed a classification of NMs on their dimensions, particle size, shape, and grain boundary engineering and their origins, natural nanomaterials, and synthetic or engineered nanomaterials. Within natural NMs, which are the result of photochemical reactions, volcanic eruptions, dust storms, and cosmic dust, forest fires (releasing of ash and smoke) are referred to, being emphasized how they can affect human health. Within nonnatural NMs the authors have considered the nanoparticles derived from engine automobile exhaust, in particular from diesel engines, airplane engines, fuel oil and coal for power generation, chemical manufacturing, ore refining and smelting, cigarette smoking, and building demolition which are examples of anthropogenic activities that led to NP and NM formation and that they may induce adverse both in the environment and human health. Particularly in cities and towns, the main source of atmospheric nanoparticles is automobile exhaust (Kagawa 2002). More than 90% of carbon NPs present in the atmosphere are diesel-generated particles (Kittelson 2001).

Mostly NPs used for commercial applications are engineered NPs that are produced using physical (Cao 2004), chemical (Hyeon 2003), and biological methods (Mohanpuria et al. 2008).

Surprisingly clay minerals and clays, as natural and abundant nanoparticles and nanomaterials, did not deserve a simple reference and comment in the article written by Jeevanandam et al. 2018 that we consider a landmark in the scientific and technological fields of both nanoparticles and nanomaterials.

Clay minerals and other minerals can be the basic constituents of diverse and technologically important nanostructured materials, such as ceramics, paper, paints, cosmetics, pharmaceuticals, biomedical devices and applications, etc. Nanostructured materials based on nanoparticles constitute fundamental components of the human body: bone, proteins, enzymes, and even in the DNA, and without them the normal human body functions would be impossible.

The bone, for instance, is a nanostructure composed of inorganic hydroxyapatite crystals and organic collagen fibers, organized in a way to form the trabeculae and osteon units (Gong et al. 2015).

In the natural environment, the nanoparticles of origin both geogenic and anthropogenic are everywhere, in the soil, in the air, and in the water, and when they interact with the human body, they can be incorporated through ingestion, inhalation, and dermal absorption.

In general, nanoparticles toxicity is being considered with great interest, although with uncertainties and partial understandings, necessitating further epidemiological studies (Neil et al. 2006; Cameron and Mitchell 2007; Jeevanandam et al. 2018).

It is in the effects of inhalation through the respiration of nanoparticles, particularly when they have diameters smaller than 50 nm, that epidemiological studies are more developed. Dockery et al. (1993) related the morbidity observed in certain US cities with episodes of air pollution and the inhalation of nanoparticles, mainly sulfates. The atmosphere carries suspended natural nanoparticles from soil, volcanic emissions, and marine aerosols, but those living in urban and industrial areas suffer the effects of anthropogenic nanoparticles. Once deposited throughout the respiratory tract, the finer nanoparticles can enter the circulatory and lymphatic system, depending on the toxicity of the specific surface and composition.

As nanominerals are geomaterials, the concept of nanomaterial naturally encompasses the concept of nanomineral. As aforesaid the definition of nanomaterial has generated in the scientific-technological community some controversy, particularly regarding the origin and the dimensional limits of the nanomaterials, reason why the

European Commission, in 2011, recommended the following definition of *nanomaterial*:

> Natural, incidental or manufactured material containing particles in a disaggregated state, or in an aggregated state, or in an agglomerated state, and which in relation to the dimensional distribution of the particles (number/size in %) 50% or more of the particles have one or more dimensions external in the range 1–100 nanometers.

Unlike the other materials whose properties, in general, depend on the respective physicochemical composition and the environment at the interface (physical state, temperature, pressure), the properties of the nanomaterials are mainly due to the reduced size of their particles and to modifications at the level of the structure which lead to the increase of the surface area with respect to the volume, consequently increasing the number of atoms/molecules on the surfaces. They are the surface properties of nanomaterials that modify their reactivity, often improving mechanical, electrical, magnetic, and optical properties compared to materials with the same physicochemical composition but with larger particles.

Nanoscience studies the phenomena that govern the behavior of atoms, molecules, and atomic and molecular structures in the manometric scale. *Nanotechnology* consists of the application of nanoscience to the control and manipulation of the structured matter at the atomic and molecular level allowing the development of devices, functional materials, and systems (e.g., of drug delivery) with properties significantly different from those observed in the micro/macroscopic scales.

Current and growing interest in *nanoscience* and *nanotechnology* is having strong scientific, technological, and economic impacts.

In the so-called nanotechnology, a set of recent development technologies considered twenty-first century technologies that require interdisciplinary intervention; nanominerals and nanomaterials are prepared to be used for example in pharmacy, cosmetics and medicine. Nanoparticles are potential nanocarriers for direct cell/tissue delivery of therapeutic or diagnostic compounds.

The so-called nanominerals, natural or modified clay minerals included, also play important roles in the field of nanomedicine defined as the science and technology of diagnosing, treating and preventing disease and traumatic injury, relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body.

Nanominerals embrace five main disciplines which are in many ways:

1. Overlapping and are underpinned by common technical issues
2. Nanomaterials and devices
3. Analytical and imaging tools;
4. Novel therapeutics and drug delivery systems
5. Clinical applications
6. Safety and toxicological issues (environmental, manufacturing, and clinical use) (ESF-European Medical Research Councils report 2004)

Nanominerals are represented by the inorganic nanotubes, such as carbon nanotubes, halloysite nanotubes, and allophane and *imogolite nanospherules* and *tubules*, which have been thoroughly investigated as drug delivery systems. Other inorganic nanotubes, particularly based on transition metal chalcogenides, are known: tungsten and molybdenum disulfides, boron nitride, titanium dioxide, alumina, silicon, and others. Particle size is an important factor for good absorption of minerals, for example, when using mineral and vitamin supplements. It is recognized that the smaller the size of a particle, the larger its surface, the surface that the human body uses to decompose and absorb the nutrients. The larger the surface of the particles, the better the nutrients can be used.

According to Das et al. (2013), three groups of nanomaterials have much applied interest:

1. Zero-dimensional materials, the so-called quantum dots, with variations in shape and size
2. One-dimensional materials, including so-called nanorods and nanowires
3. Two-dimensional materials, including nanodiscs, nanofilms and nano-foils.

Still according to Das et al. (2013), in the last two decades, the high number of manufactured nanomaterials was developed for diagnostic and therapeutic applications. For diagnostic applications, nanoparticles enable detection at the molecular scale. Effectively some fluorescent nano hybrids may serve the dual purpose of detecting and destroying pathogenic microbes.

The specificity and sensitivity of magnetic resonance imaging can still be greatly improved by the use of nanoparticles as a material to bring about contrast. Particle size is an important factor for good absorption of minerals, for example, when using mineral and vitamin supplements. It is recognized that the smaller the size of a particle, the larger its surface, the surface that the human body uses to decompose and absorb the nutrients. The larger the surface of the particles, the better the nutrients can be used.

For therapeutic applications, the nanoparticles must be biocompatible and synthesized by simple methods and should allow the drug to be delivered to the target and the sustained release of the drug molecules and must also have great potential in so-called tissue engineering.

Nanoparticles are the basis of biosensors, of contrast imaging enhancers, and of nanomaterials used in drug delivery. It is called *modified drug delivery* when the dose in a pharmaceutical form is designed to provide the therapeutic levels of the drug where it should act and maintain those levels throughout the treatment (*In*: Ding et al. 2002).

The book entitled *Biomedical Applications of Nanoparticles* and issued in 2019, Grumezescu AM being the editor, covers and enhances the biomedical applications of various types of nanoparticles.

About one dozen of nanomaterials with therapeutic interest, the so-called nanomedicines, are currently licensed. These are ingenious devices or "machines" that will revolutionize medicine in the near future. They are small enough to flow through our arteries and veins but are packed with clever nanotechnology to identify the cause and remedy for the disease.

The simplest nanomedications are spherical particles, smaller than human cells or bacteria but larger than individual molecules, which contain a “load” of chemicals and are small enough to penetrate cells.

Nanomedicines are large enough to stay in the bloodstream for longer than conventional drug molecules, though not so large as to be able to clog blood vessels. Scientists may even attach biological molecules to the exterior of the nanoparticles to ensure, for example, that they are attracted to specific body molecules such as those found in tumors.

Some nanodevices may allow the cell membrane to be punctured in much the same way as a virus injects its DNA to infect a host cell. Discovering the ability to deliver “chemical charge” at the affected site, recognizing the affected molecules, and recognizing the ability to drill the cells, scientists could create nanodevices able to move to the site of the tumor and treat it directly.

Controlled drug delivery has been extensively studied in order to improve drug efficiency and patient compliance and also to reduce drug toxicity. Nanodevices for these purposes are particularly useful in the treatment of chronic conditions because they provide time profiles of effective drug concentration in the plasma, keeping the drug concentration constant within the therapeutic time interval (Gallo et al. 2013).

Scientists also hope nanomedicines can be used to send signals about conditions in the human body. For example, nanoparticles known as “quantum dots” have an inner metal core and a protective shell, which gives them unique optical properties that allow the modification of the nanoparticles in order to emit fluorescent light in the presence of a certain disease, after which the situation is monitored by a scanner.

Scientists generally classify nanomedicines into two groups: “hard” and “soft.” Among the well-known and developing nanodevices, there are those with an organic basis (“soft”, others with an inorganic “hard” base).

Nanotechnological materials and systems employed in the *targeted delivery of drugs* for treatment of, for example, tumors can be classified into the following groups:

1. Tensiometers
2. Lipids
3. Polymers
4. Inorganic

The last group – inorganic – comprises minerals such as carbon nanotubes, metals (gold and silver), and clay minerals, *halloysite* tubes in particular.

The book entitled *Natural Mineral Nanotubes: Properties and Applications* published in 2015 by AAP (Apple Academic Press) and CRC Press (Taylor & Francis Group) and Pasbakhsh P and Churchman GJ (editors) for example in health, of certain clay minerals, in particular those which present themselves as nanotubes, as is the case with the clay mineral *halloysite*.

Aguzzi et al. (2006) discuss the possibilities and limitations of clay-containing systems for the purposes of drug delivery and Viseras et al. (2010) present the current challenges regarding the use of clay minerals for drug delivery.

10.2 Types and Characteristics of Nanominerals and Nanomaterials

Some of the devices or “machines” that are small enough to “travel” inside the human body, and can for example eliminate tumors, are referred and characterized as follows:

10.2.1 Polymeric Particles

In the recent decades, polymeric particles have been widely used as biomaterials due to their favorable properties, biocompatibility, easy design and preparation, varied structures, and biomimetic character.

Polymeric particles are being used for the encapsulation of drugs or cosmetic ingredients; the encapsulation enables the transport of the active substance to the site of action (the active ingredient may also be a cosmetic ingredient) and provides sustained and controlled release of the drug and stabilization of the active substance in the body; as a rule, microparticles (100–500 nm) designed for parental administration are used; the polymers are generally biocompatible and biodegradable polyesters.

Bennet and Kim (2014) and Keller et al. (2019) show relevant information on biomedical applications of polymeric particles.

10.2.2 Liposomes

Liposomes by definition are sphere-shaped vesicles consisting of one or more phospholipid bilayer, being first described in the mid-1960s.

Liposomes are the most common vectors for transporting drugs; they can be loaded with either hydrophilic ingredients or lipophilic ingredients; they are hollow nanospheres whose interior can be filled with a drug; nanospheres are made of the same type of lipids that are present in the stratum corneum and the material of the two-layered phospholipid cell membranes; the outer face is hydrophilic, and the inner face is hydrophobic; since the surfactants, generally phospholipids used in the preparation of the *liposomes*, are similar to those found in the skin, the liposomes can readily be mixed with the stratum corneum intercellular lipids; the phospholipids are nontoxic, and their incorporation into the stratum corneum layers modifies the composition of the lipid mixture and may alter the permeability of the skin.

Akbarzadeh et al. (2013) present the *liposome* classification, preparation, and application.

According to Wacker (2019), the Pharmaceutical Science has indisputably become more complex with the discovery of nanocarrier-based delivery systems.

Fueled by first successes in the 1990s, *liposomes* were at the forefront of cancer therapy (Barenholz 2012; Wacker 2013). The challenges associated with their characterization earned them the name “nonbiological complex drugs” (NBCDs). Nowadays, there is broad acceptance for liposomal drugs as a niche product, but we still do not know much about the attributes that enable targeted delivery in humans.

10.2.3 Micelles

Micelles are structures composed of two immiscible liquids (oil and water) and a surfactant that, due to its composition, is capable of interacting simultaneously with both liquids.

Cagel et al. (2017) state that *polymeric micelles* are drug nanocarriers that exhibit several in vitro and in vivo advantages relatively to other drug nanocarriers, as well as increased stability and solubility to hydrophobic drugs. The authors show that the properties of polymeric micelles can be optimized and some of their disadvantages can be overcome by the combination of two or more polymers in order to assemble polymeric mixed micelles. Also, the authors provide an overview on the current state of the art of several mixed micellar formulations as nanocarriers for drugs and imaging probes, evaluating their ongoing status (preclinical or clinical stage), with special emphasis on type of copolymers, physicochemical properties, in vivo progress achieved so far, and toxicity profiles.

Cabral et al. (2018) state that *polymeric micelles* are demonstrating high potential as *nanomedicines* capable of controlling the distribution and function of loaded bioactive agents in the human body, effectively overcoming biological barriers, and various formulations are engaged in intensive preclinical and clinical testing. According to the authors, to elicit a given therapeutic response, the indispensable amount of active drug should reach its site of action, while the effective dose must be maintained at the target site for a definite time. However, for most drugs, such a process poses several inexorable barriers, including their fast degradation in the harsh in viv*o* environment, inadequate pharmacokinetics, lack of selectivity for the targeted tissues, and widespread biodistribution after systemic administration, which is a potential cause of toxicity. For example, most anticancer drugs are water-insoluble molecules with low-molecular weight (MW), which distribute to the whole body after intravenous injection, critically limiting the dosage due to the underlying risk of side effects, while proteins and genes, designed as therapeutic agents, present unfavorable pharmacokinetics and poor internalization by targeted cells and are rapidly degraded.

The use of *polymeric micelles* as targeted nanomedicines can overcome these constrains, controlling the spatiotemporal distribution of drugs, as well as avoiding side effects; such *micelles* could be designed as effective approaches to satisfy unmet medical demands or constitute the foundation for unprecedented or revolutionary treatments.

10.2.4 Emulsions

Emulsion is the name given to the dispersion of two immiscible liquids by the formation of micelles.

Emulsions are made from tiny droplets or droplets of oil (or water) dispersed in water (or oil). The droplet size of the emulsions is often greater than 1 μm, but there are nanoemulsions whose droplets have a diameter varying between 100 and 300 nm and are prepared using a very potent dispersion process.

Emulsions are widely used in cosmetic formulations. Due to their liquid nature, the droplets of the emulsion do not penetrate intact into the skin and disintegrate on the surface of the skin, and its ingredients penetrate the skin as individual molecules.

10.2.5 Carbon Nanotubes

Carbon nanotubes (CNTs) are sheets of graphene with the thickness of a carbon atom, rolled up to form small and narrow tubes (nanotubes). Carbon nanotubes were discovered in 1991 by Iijima, a Japanese scientist.

Carbon nanotubes (CNTs) are allotropes of carbon, made of *graphite* mineral, and constructed in cylindrical tubes with nanometer in diameter and several millimeters in length.

According to He et al. (2013a, b), CNTs are characterized by their impressive structural, mechanical, and electronic properties due to their small size and mass, their strong mechanical potency, and their high electrical and thermal conductivity. CNTs began to be used as additives in various structural materials, electronic, optical, and plastic, among others. Only in the beginning of the twenty-first century, CNTs were introduced into pharmacy and medicine for therapies based on *drug delivery systems*.

CNTs can adsorb a wide variety of therapeutic molecules and have proved to be excellent vehicles for drug delivery by direct penetration into cells and maintenance of intact drug without metabolization during transport in the body.

He et al. (2013a, b) present a very interesting review of the current knowledge of the different applications of carbon nanotubes in pharmacy and medicine and of the methodologies that use nanotubes as vehicles for transporting drugs and biomolecules in the treatment and diagnosis of feared diseases. For these authors, the discovery of bionanotechnologies involving the use of carbon nanotubes has opened new and more efficient alternatives to the previously practiced methods of drug delivery, since carbon nanotubes can cross cell membranes and transport drugs, genes, biomolecules, vaccines, etc. to the interior of the target cells or even organs not reachable previously.

CNTs have been successfully applied in pharmacy and medicine due to their high surface area that is capable of adsorbing or conjugating with a wide variety of therapeutic and diagnostic agents (drugs, genes, vaccines, antibodies, biosensors, etc.). They have been first proven to be an excellent vehicle for drug delivery directly into cells without metabolism by the body. Then other applications of CNTs have been extensively performed not only for drug and gene therapies but also for tissue regeneration, biosensor diagnosis, enantiomer separation of chiral drugs, and extraction and analysis of drugs and pollutants. CNTs have applications in cancer therapy and imaging. CNTs can be used at the tip of a nano needle so that specific substances can be injected into specific areas of individual cells.

10.2.6 Gold Nanoparticles

The mineral gold and the metal gold were one of the first to be discovered by man who, for thousands of years, has been giving varied uses.

According to Dykman and Khlebtsov (2011), the first information on the medicinal use of colloidal gold was found in Golden, Arab, and Indian (liquid gold) books with references to the V–IV century B.C.

In Europe, it is only in the Middle Ages that there are references to investigations of colloidal gold by the alchemists.

Paracelsus (1493–1541) produced writings on the therapeutic properties of gold called "fifth essentia auri" having used "aurum potabile" in the treatment of mental and syphilis diseases. In 1583 the alchemist David de Planis-Camp physician of Louis XIII of France recommended his "elixir of longevity," a solution in water of colloidal gold.

The first book on colloidal gold referring to the process of its production and applications in medicine was published in 1618 by the physician and philosopher Francisco Antonio. Also, the English botanist Nicholas Culpepper, in 1656, published a book where he refers and discusses the medicinal uses of colloidal gold. The use of gold nanoparticles in biological studies based on immunochemistry only occurred in 1971 by the British researchers Faulk and Taylor (1971).

The nanometric size of colloidal gold, its nontoxicity, and its non-immunogenicity make it used in the detection of diseases such as cancer and in its treatment by chemotherapy and radiotherapy. Gold nanoparticles can enhance the effects of radiotherapy. Gold nanoparticles have unique optical properties, are easy to use with different biomarkers in aqueous solution, and are able to efficiently transfer electrons between different electro-active species and electrodes.

There are three main types of biosensors based on gold nanoparticles: otic, electrochemical, and piezoelectric.

Gold nanoparticles are used as a contrast agent in the diagnosis, for example, of heart disease and cancer. As a result of the high SPR ("surface plasmon resonance"), gold nanoparticles can absorb strongly light, and, if the light wavelengths are between 700 and 800 nm, absorbed light can be efficiently converted into heat, which makes gold nanoparticles useful in photothermal therapies in the case of cancer and other diseases.

Ghosh et al. (2008) provide good evidence of the importance of gold nanoparticles in nanodrug delivery systems whose efficiency is optimal when they ensure that the active drug is available at the site of action for the correct time and its concentration is above the minimum effective concentration and below the minimum toxic concentration.

Huang and El-Sayed (2010) present information on the implementation of the use of gold nanoparticles in the diagnosis of cancer and in the therapy to combat it called photothermal therapy. Also, Dykman and Khlebtsov (2011) present an excellent and very current review of the medical applications of gold nanoparticles.

10.2.7 "Quantum Dots"

The name "quantum dots" is assigned to a portion of matter so small that it is actually concentrated at a single point, and the particles that form that matter and carry electricity are trapped and have well-defined energy levels in accordance with the laws of quantum theory, like individual atoms. "Quantum dots" are tiny beads or rather small enough crystals (containing hundreds to a few thousand atoms) capable of passing through the cell membranes and having an inner metal core and an outer shell; some "quantum dots" emit light that can serve to signal the presence of a disease.

The properties and applications of the "quantum dots" are well presented by Wang and Hu (2014) and by Bagher (2016).

"Quantum dots" can be used in medical imaging techniques such as fluorescence imaging. Iron oxide nanoparticles are used in magnetic resonance imaging or computer tomography.

10.2.8 Viruses

Viruses are natural nanomachines consisting of a genome and a capsid usually having a lipid envelope over it. Viruses are normally composed of proteins and DNA strands. Because of their nanosize dimensions, viruses are considered as naturally occurring nanoparticles.

Virology is the science of studying viruses, which can cause diseases in humans, animals, and plants. Viruses can infect the host cells to replicate. However, plant viruses are not infectious toward mammals and as so to humans. Most of the viruses being used have origin in plants. *Tobacco mosaic virus*, for instance, and other plant derived viruses have been used in drug sustained delivery, in vaccines, in immunotherapy interventions, and imaging applications.

In the literature a significant number of scientific articles are available particularly on applications of viral nanoparticles in medicine (Yildiz et al. 2011; Steinmetz 2013; and Shoeb and Hefferon 2019). Since 1970s viruses have been used as vectors for the benefit of humans, in gene therapy, and in cancer control and therapy. Equipping existing viruses with medical functions is a promising area of medicine.

According to Bolzinger et al. (2011) in society is growing anxiety about nanotechnologies and, more particularly, about the toxicity and risks of nanoparticles. Effectively, it is assumed that nanoparticles can penetrate the body due to their small size and strong reactivity, overcoming the various biological barriers (Borm et al. 2006). There are two pathways for the entry of nanoparticles into the human body: oral and cutaneous. As a consequence of this assumption, all types of nanoparticles are suspected of possible health effects.

Several reports and compilations of scientific information published in the European Union and the USA in 2005–2006 have concluded that the available information does not confirm the risks to human health of nanoparticles; this is the case with the SCENIHR report (2005) of the European Commission.

Nanoparticle penetration into the skin involves to go beyond the *stratum corneum* barrier and reach the viable layers of the skin: epidermis and dermis. For this purpose, three routes are allowed:

1. Intercellular via the *stratum corneum* lipids.
2. Intracellular via the corneocytes; and, for this purpose, the intercellular lipids must pass from a corneocyte to another corneocyte.
3. Through the pilosebaceous follicles, it seems to be the easiest route, yet it has to overcome a membrane before the inner layers of skin are reached.

10.2.9 Halloysite Nanotubes

Halloysite is a clay mineral that with other clay mineral species belongs to the kaolin group in the clay systematics. The physicochemical properties of halloysite are well characterized by Yang et al. (2016). The *halloysite nanotubes* (HNTs) are naturally occurring tubular clay nanomaterials made of aluminosilicate kaolin layers rolled several times; the aluminol and siloxane groups on the surface of HNT facilitate the formation of hydrogen bonding with the biomolecules onto its surface. These crystallochemical characteristics can provide interesting applications in biomedicine and nanomedicine, namely, drug delivery, gene delivery, tissue engineering, cancer and stem cell isolation, and bioimaging (Satish et al. 2019).

Halloysite is a clay mineral that is biocompatible but is not biodegradable and is therefore not suitable for intravenous administration or for oral administration; its application in medicine is limited to biomedical devices.

Some authors have studied the properties and applications of nanotubes of *halloysite* in nanomedicine: Veerabadran et al. (2007), Vergaro et al. (2012), Ward et al. (2012), Guo et al. (2012), Pasbakhsh et al. (2013), Liu et al. (2014a, b, 2016a, b), Lun et al. (2014), Tan et al. (2014), Abdullayev (2015), Abdullayev and Lvov (2016), Churchman and Pasbakhsh (2015), Cervini-Silva et al. (2015), Duce et al. (2015), Yendluri et al. (2017), Aguzzi et al. (2016), Massaro et al. (2017, 2018a, b), Ghezzi et al. (2018), Satish et al. (2019), Detellier and Schoonheydt (2014), Du et al. (2010), Ghorbanpour (2016), Grumezescu (2019), Hanif et al. (2016), Hári et al. (2016), Jin et al. (2016), Lagaly (1984), Letaief and Detellier (2013), Liu et al. (2011, 2012), Lvov and Price (2015), Lvov et al. (2016), Mousty (2004), Pasbakhsh et al. (2016), Pierchala et al. (2018), Price et al. (2001), Soule and Burns (2001), Veerabadran et al. (2009), Viseras et al. (2015), Wilson and Keeling (2016), and Yuan et al. (2015, 2016).

Lamellar particles of *kaolinite* itself can be transformed into nanotubes after being submitted to intercalation, delamination, and washing. In nature there are intermediate morphological forms between the planar shape of kaolinite crystals and the rolled shape of halloysite crystals. Also, in nature halloysite tube lengths are variable (generally in the range 0.2–2 μm), those in the sub-nanometer range being the most favorable for applications in nanomedicine.

Regarding *allophane* nanotubes, particularly in the last decade, much research has been conducted and published on its use as a locally controlled transport, encapsulation, and delivery vehicle of chemically and biologically active agents, potential drugs, to combat, for example, cancer cells.

Halloysite, $Al_2Si_2O_5(OH)_4.nH_2O$, where *n* ranges from 0 to 2 (the value 2 corresponds to the maximum hydration expressed by a slide of water molecules positioned between structural layers) is a clayey phyllosilicate mineral from the *kaolinite group*, $Al_2Si_2O_5(OH)_4$, differing of kaolinite from the crystallochemical point of view because the structural interlayer spaces can be occupied with water molecules and also because from the morphological point of view, in the case of the tubular halloysite variety, its particles instead of displaying are usually coiled up creating a kind of tubes or nanotubes (when the size is extremely small).

The outer surfaces of the *halloysite* tubes consist of silica or better structural sheets of negatively charged SiO groups, whereas the inner surfaces are constituted by alumina or better structural sheets of positively charged Al-OH groups, a situation which according to Yendluri et al. (2017) leads to the creation of a strongly negative zeta potential (-35 mV) on the outer surfaces, and a positive potential zeta (+25 mV) on the inner surfaces is evidenced in aqueous dispersions of pH 4–8.

The length of the *halloysite* tubes depends on the deposit in which the *halloysite* occurs and can vary between 0.2 and 1.5 μm. The thickness of the tubes comprises 10–15 structural layers (each constituted layer is a structural sheet of SiOH groups or "siloxane groups" on the outer surface attached to a structural sheet of AlOH groups or "aluminol groups" on the inner surface). The internal and external diameter of the tubes can vary between 10–30 nm and 40–70 nm, respectively. The inner lumen diameter of the nanotubes allows the incorporation of chemical agents with medicinal interest.

Halloysite holds a unique position among nanomaterials and nanoclays used for controllable loading and release of active agents such as drugs. The loading efficiency is closely related to the size of the lumen of halloysite tubes, a factor that commands its effective pore volume (Abdullayev and Lvov 2016). *Halloysite nanotubes* have been successfully loaded with diverse types of active agents, such as drugs, antibacterials, and mold growth inhibitors, made of simple organic and inorganic substances, as well as enzymes and proteins having relatively large molecules.

Halloysite entraps molecules in three different ways:

1. Adsorption to the external and internal walls of the tubes
2. Loading into lumen
3. Intercalation between structural layers (Abdullayev and Lvov 2013, 2016; Lvov and Abdullayev 2013)

10.2.10 Nano Spherules and Tubules of Allophane and Imogolite

Allophane and *imogolite* are poorly crystalline or short-range crystalline order hydrous aluminosilicates, the first made of nanometric hollow spherules, the second of nanometric tubules. In recent years there has been significant research on applications of these minerals as catalysts and catalytic carriers (Theng 2012). In addition, it is important to note that these minerals have been used in the treatment of human health.

Imogolite occurs naturally in the soils of some weathered volcanic rocks. Typically, it is composed of single-walled aluminosilicate nanotubes with an external and inner diameter of approximately 1.0 nm. *Imogolite* tube walls consist of a curved gibbsite-like sheet, $Al(OH)_3$, where the inner hydroxyl surface of the gibbsite is replaced by $(SiO_3)OH$ groups (Guimarães et al. 2007; Guimarães et al. 2013). Imogolite chemical composition is expressed by $(HO)_3Al_2O_3SiOH$.

Both natural and synthetic *imogolite nanotubes* are easily dispersed in water where they keep their outstanding one-dimensional morphology, and light-scattering studies showed that they remain rather stiff in aqueous dispersion. *Imogolite nanotubes* usually have very large aspect ratios, which typically range from 100 to 1000. Hence, aqueous dispersions of *imogolite nanotubes* are very good candidates to display liquid crystalline phases. Indeed, the liquid crystalline properties of *imogolite* dispersions were already recognized more than 30 years ago by a Japanese team of researchers (Kajivara et al. 1986a, b).

Samples of aqueous dispersions of *imogolite nanotubes*, in a given range of concentrations and held in test tubes left standing under the influence of gravity, spontaneously demix into two different phases within a few days. First, *imogolite nanotubes* have a very large aspect ratio because they are both very long and stiff. Indeed, not only is their overall length (also called the “contour length”) very great compared to their diameter, but their persistence length is as well, owing to their low flexibility.

Thanks to their huge aspect ratio and good mechanical properties which are fairly comparable to those of carbon nanotubes, *imogolite nanotubes* have emerged as an interesting possibility for mineral particles to prepare CPN. Indeed, one of the present issues in this field is to reduce the amount of filler while preserving the desired properties of the composite materials. For this purpose, highly anisotropic particles are sought after in order to reduce their percolation threshold. Moreover, achieving macroscopic alignment of the particles is often useful to reduce the viscosity of the mixtures involved in processing the nanocomposites and to obtain anisotropic physical properties. Early reports of imogolite-based nanocomposite materials were published by a Japanese group that investigated mixtures of imogolite nanotubes with either hydroxypropylcellulose (HPC) or poly (vinyl alcohol) (PVA) (Hoshino et al. 1992a, b).

As a concluding remark, the great progress of nanoscience and nanotechnology, particularly in the last decade, has led to the study and the construction of advanced nanomaterials based on organic and inorganic materials.

A particular reference is due to the 11 volumes of a series entitled “Applications of Nanobiomaterials” produced by Elsevier, Grumezescu AM being the editor, with contributions of scientists from all over the world; volume 8 deals with the subject “Nanobiomaterials in Medical Imaging.”

10.3 Basic Data on Organoclays: Preparation, Properties, and Biomedical Applications

Organoclay, an artificially synthesized engineering material, has increasing usages in a variety of barrier systems, such as landfill clayliner, vertical cutoff wall, slurry wall, and cover system (Sharma and Reddy 2004).

Organoclays are mainly based on *smectite* clay minerals and less on *sepiolite* and *halloysite*; they have been extensively used in environmental *applications, particularly in pesticide formulations able to avoid or reduce the* loss of bioactivity due to volatility or photodegradation of insecticides and herbicides associated to the organoclay; another important application is the removal of pollutants, particularly those of organophilic character; new trends contemplate the use of nontoxic modifiers of biological origin instead of the conventional surfactant quaternary ammonium-based agents, able to be used in biomedical applications (e.g., biopolymer-clay nanostructured hybrids, i.e., the so-called bionanocomposites, to produce scaffolds for tissue engineering).

Compared to unmodified natural clays, *organoclays* have enhanced physical and physicochemical properties, including hydraulic conductivity, sorptive capacity, swelling index, suspension stability, strength, and stiffness.

Lagaly et al. (2006) produced an article titled “Clay Mineral Organic Interactions” that is considered a basic milestone in regard to both fundamental and applied fields of clay mineral-organic compound interaction. Such interaction has been early used to distinguish clay mineral distinction based on the intercalation of organic molecules into the interlayer spaces of clay minerals.

Within the 1:1 clay minerals, only the mineral species of the *kaolinite group* were reactive to the intercalation of various organic compounds such as urea, formamide, potassium acetate, ammonium acetate, hydrazine, and dimethyl sulphoxide, following the replacement of the interlayer bonding made of hydrogen bonds and van der Walls forces by the hydrogen bonds of those organic compounds; on the contrary, the species belonging to the serpentine subgroup were nonreactive. Kaolinite structural order-disorder and particle size are conditioners of the intercalation degree.

Within the 2:1 clay minerals, polar organic molecules such as alcohols, amines, amides, ketones, aldehydes, and nitriles form intercalation complexes with the clay minerals of the *smectite group*; in the case of neutral molecules, intercalation and adsorption are driven by various chemical interactions: hydrogen bonds, ion-dipole interaction, coordination bonds, acid-base reactions, charge-transfer, and van der Walls forces.

Intercalation of ethylene-glycol and glycerol in expanding 2:1 clay minerals is widely used for routine identification and distinction of smectites from vermiculites. The interlayer cations of smectites and vermiculites can be exchanged by organic and organometallic cations in solution and in the solid state, the cation exchange reactions being performed by mixing aqueous dispersions of clay mineral and a solution of organoammonium salt (e.g., alkylammonium salts). Quantitative exchange of the interlayer cations of smectites by alkylammonium ions provides a method for characterization of smectites and vermiculites and determination of their layer charge (Lagaly 1981 1994; and Mermut and Lagaly 2001).

The studies reported by Lagaly et al. (2006) were fundamental for the understanding of the mechanisms of clay-organic interactions and open the way to the production of advanced materials for industrial, environmental, biomedical, and pharmaceutical applications.

Ruiz-Hitzky et al. have produced an interesting article about organoclays, including historical information, concepts, and applications. The authors mentioned that the first clay-organic complex, classified as an environmental application, was used in Ancient Rome of the mixture clay/decaying urine, very efficient in laundry processes; the needed urine was collected in public urinals. The authors too have considered the so-called Maya Blue pigment as one of the first nanostructured hybrid clay-organic compound, used by the ancient Maya civilization in pottery and murals from about 300 to 1500 A.D., characterized by its persistent color stability in one of the harshest climates. The color is resistant to extremes of pH, chemical solvents, and bio- and photodegradation. Today, it is known based on the research carried out by several researchers that the pigment is a nanorganoclay, more precisely a hybrid organic-inorganic nanomaterial composed of the clay mineral *palygorskite* and a natural dye, *indigo*, extracted from certain plant, the preparation process being proposed by Arnold (2005) and Arnold et al. (2008).

The resistance of “Maya Blue” to acids is not due to the role of the indigo but to the role of the clay (Sanchéz del Rio et al. 2006). The indigo molecules are attached at the openings of the channels existing in the structure of palygorskite and became anchored by hydrogen bonds to the silanol groups.

Sanchez et al. (2005) made a review focused on applications of hybrid organic-inorganic nanocomposites. Regarding “Maya Blue” the authors consider that it is an example of a hybrid organic-inorganic nanocomposite, the molecules of natural blue dye indigo being encapsulated into the structural channels of *palygorskite*.

Still, according to Ruiz-Hitzky et al. (2010), the researchers Gieseking (1939) and MacEwan (1948) had been the pioneers in the field of systematic preparation and characterization of organoclays using modern techniques based on the intercalation of *montmorillonite* with quaternary ammonium species and neutral polar molecules, respectively. In the case of *montmorillonite,* the inorganic exchangeable cations, as a rule Na^+ and Ca^{2+} occupying interlayer positions, can be replaced by organic cations, for instance, long-chain alkylammonium cations, through ion exchange reactions, the bonding mechanism between the organic cations and the negatively charged internal surfaces of the clay mineral structural layers being essentially electrostatic. Even biological cationic large molecules such as chitosan can be incorporated in organophilic clay minerals.

X-ray diffraction is the currently used analytical technique to identify the incorporation and arrangement of the organocations in the interlayer spaces.

The name *nanoclay* is attributed to clay mineral modified by the incorporation of organic cations. The name *nanocomposite* is attributed when the modifiers are polymers, and within nanocomposites the name *bionanocomposites* is attributed to an emerging group of biohybrid materials derived from the assembly of clay minerals and other inorganic solids with naturally occurring or bio-based polymers, for instance, starch, cellulose and its derivatives, chitosan, gelatin, or biopolyesters such as polylactic acid. Besides organoclays based on clay minerals exhibiting planar structure, organoclays can be prepared too using clay minerals exhibiting fibrous structure, such as *palygorskite* and s*epiolite*.

Various and important applications in the environment field have been developed based on the high sorption capabilities of nanoclays for both cations and anions, for instance, in water treatment, waste disposal liners, and pesticide carriers. Also, various and important research papers on biomedical applications of nanoclays have been produced particularly in the last decade, from tissue engineering to drug delivery systems (Choy et al. 2007; Katti et al. 2008; Viseras et al. 2008; Fakhrullin and Lvov 2016; Bonifacio et al. 2017; Zhang et al. 2018; and Viseras et al. 2019). In spite of its growing popularity, previous studies on *organoclays* are limited to one or a few particular properties. *Organoclays* are organic-rich clay minerals, synthesized under controlled laboratory conditions, with engineering properties enhanced for use in containment applications.

Organoclay is composed of two components, one inorganic, the other organic, respectively, known as (**1**) the inorganic base clay and (**2**) the organic compound.

Clay minerals are responsible for the fixation and eventual immobilization of biomolecules on crystal surfaces of natural clay minerals. *Montmorillonite*, which is the major clay mineral species that composes bentonite, is the most often used base clay. Other clay minerals, such as *hectorite*, *synthetic fluorohectorite*, *synthetic micas*, *sepiolite*, illite, *muscovite*, *kaolinite*, and *vermiculite*, have been also used as the base clay (de Paiva et al. 2008).

The net negative electric charge of *montmorillonite* structural layers dominant on basal surfaces and the pH-dependent negative (for high pH) and positive (for low pH) charge developed on broken edges originate the surface reactivity of the clay mineral. Thus biomolecules, either negatively or positively charged, can be immobilized on basal surfaces, edges, or interlayer/microchannels of clay particles (Ghadiri et al. 2015; Alcântara et al. 2014).

The adsorption of organic biomolecules on clay minerals includes hydrophobic interactions, hydrogen bonding, protonation, ligand exchange, cation exchange, cation bridging, and water bridging (Oliveira et al. 2018). The organic components used in organoclays include quaternary ammonium cations (QACs; a type of surfactants), many other organic compounds (i.e., polymeric quaternary alkylammonium salts and copolymers, alcohols, and aldehydes), biomolecules (i.e., proteins, enzymes, amino acids, and peptides), and proprietary agents in commercial products (de Paiva et al. 2008; Bate et al. 2014; and Lee et al. 2012). Among them, QACs are the most used organic compounds for organoclays (de Paiva et al. 2008; Sarkar et al. 2012), and the properties of QAC-modified organoclays are the major components of this review paper.

Organoclays were most often synthesized by cation exchange reactions in aqueous solution, although neutral organic compounds can also be adsorbed by other driving forces. Alternatively, solid-state reaction was also used in several studies (de Paiva et al. 2008), where dry organics and clay minerals were mixed mechanically, sometimes with elevated temperature (Breakwell et al. 1995).

For organic molecules with polar groups, the negative parts of the polar groups attract cations on the surface of clay mineral and displace surrounding water molecules. This reaction is named ion-dipole interaction (de Paiva et al. 2008). Solid-state reaction has the advantages of being environment-friendly and suitable for industry production (de Paiva et al. 2008).

Microstructural changes occur in the organically modified clays. Essentially, the interlayer species controls the sorption and osmosis potential in the organoclays, while the surface species controls the interparticle forces, stability of suspended particles, electrokinetics and fluid conduction. Therefore, the surface properties and interlayer microstructure of the clayey barrier material are highly relevant to its physical and chemical properties and, ultimately, the barrier performance. In this section, the fundamentals of organic surfactant morphology and organoclay surface characteristics will be discussed, followed by their relevance and impact to the organoclay barrier performance.

Due to the availability of data, and the simplicity of discussion, quaternary ammonium cations were chosen as representative organic surfactants. *Montmorillonite* is often used too as the base clay for a barrier material because of its high net surface charge, high surface area, and submicron size.

Numerous models on the ion (charges) distribution near the surface of an often negatively charged clay mineral in aqueous environment have been proposed as elaborated in Stumm and Morgan (1996) and Israelachvili (2011).

The general features of those models are as follows:

1. Immediately next to the clay mineral surface is a thin layer (about a few molecules thick) of ions and water molecules, both with limited mobility; the major-

ity, if not all, of the ions are positively charged; the water molecules are called surface-bound water; this layer is often termed Stern layer (or Helmholtz plane).

2. Outside of the Stern layer and inside of the bulk fluid, charge-balancing ions accumulate and render a cloud consisting of predominant positively charged ions (cations) and fewer negatively charged ions (anions) (Stumm and Morgan 1996); this cloud is termed the electrical diffuse layer (EDL), which can be quantified by Gouy-Chapman theory; the arrangement of Stern layer and electrical diffuse layer is referred to as the *electrical double layer*; the interactions among clay particles occur primarily through the electrical double layer.

Clay minerals can be used as "nanofillers" in the important industrial field of polymer-clay nanocomposites exhibiting specific properties and functionalized applications. To produce clay-polymer hybrids, the required dispersion of clay minerals in the polymer matrices implies the previous modification of clay particles, turning them hydrophobic through the intercalation of surfactants or grafting of hydrophobic molecules.

There are two main methodologies used for the modification of clay particles: physical and chemical methods. These authors enhance the use of clay minerals such as *montmorillonite*, *laponite*, *sepiolite, hectorite*, *rectorite*, and *kaolinite* to improve the mechanical (flexural strength), thermal, and the barrier properties, also called reinforcement of polymer nanocomposites.

Filler nature, particle size, particle shape (lamellae, tube, or fiber), particle aspect ratio, and its affinity toward the matrix polymer play a decisive role in modifying the properties (Goettler et al. 2007). Nanocomposite preparation methods include in situ polymerization, melt intercalation, and direct mixing.

Heinz (2012) produced an interesting article that reviews both chemical and physical properties of natural and organically modified clay minerals to understand their surface characteristics and application in functional nanocomposites.

10.4 Biomedical Applications of Nanomaterials

New organic-inorganic hybrid materials are currently being developed for biomedical applications, beginning with clay minerals combined with drugs intended for targeted purposes (Choy et al. 1999, 2000; Yang et al. 2003; Choy et al. 2006; Oh et al. 2006; Kim et al. 2008; Lim et al. 2011; Wang et al. 2013; Kim et al. 2016; Viseras et al. 2019; and Satish et al. 2019). Recently Kim et al. (2016) produced a very interesting review that summarizes the state of the art on the use of clay-drug hybrid materials for pharmaceutical and biomedical applications and enhances the functions, such as sustained release, increased solubility, enhanced adsorption, biocompatibility, etc., as well as the adequate methods and routes of administration. The authors point out too the challenges and future perspectives of clay mineral-based hybrids for biomedical applications. Most of the subsequent text was extracted from the aforesaid review.

Because clay minerals are efficient and safe transporters, they may provide a new paradigm in the field of drug delivery systems (DDS) compared to other inorganic materials (Suresh et al. 2010; Viseras et al. 2010, 2019; and de Sousa Rodrigues et al. 2013). Drug delivery systems have many advantages, e.g., reduced drug side effects due to sustained release and better patient compliance through reduced dose frequency.

For many types of controlled-release formulations, immediately upon placement in the release medium a large initial bolus of drug is released uncontrollably before it can reach a stable release rate (i.e., "initial burst" or "burst release"), which can result in toxicity. Drug formulations for controlling the release rate of the drug (i.e., delayed release, extended release, or sustained release) can achieve the dual target of reduced toxicity and better compliance along with enhanced drug efficacy. The incorporation of drug molecules into clay minerals has received a great deal of attention for biomedical applications because clay-drug hybrids are distinguished from simple physical mixtures of each component.

Various polar or cationic species can be combined with clay minerals by physical adsorption or intercalation to form clay-drug hybrid materials, which have the large SSA or CEC of clay minerals.

Organic drug molecules stabilized in the interlayer spaces of clay minerals could be oriented with a monolayer, bilayers, or pseudo-triple layers, or a paraffin-like monolayer or bilayer arrangement, depending not only on the CEC of the clay minerals but also on the amount of drug loaded, resulting in controlled-release and sustained-release properties. In addition, clay minerals have been utilized as formulation additives in order to enhance the solubility of poorly soluble drugs (Lim et al. 2011) to improve the photo/dispersion/thermal stability of fragile bioactive molecules, and to provide mucoadhesive properties for increasing retention time in the gastrointestinal (GI) tract and the preocular surface.

Clay-drug hybrids have also been utilized as antibacterial agents for wound healing (Meng et al. 2009; Wei et al. 2011; and Hsu et al. 2012).

Organomodified *montmorillonite* blended with a biocompatible methyl methacrylate yields a novel type of bone cement composite that improves cell growth on the bone cement surface.

The fascinating features of clay-drug hybrid materials allow the potential to develop efficient DDS. In the present review, DDS with clay-drug hybrid materials are categorized based on the methods of administration, and their advantages and therapeutic effects are summarized. The challenges and future prospects of clay-drug hybrids are described in terms of biomedical applications.

Very recently Satish et al. (2019) produced a very interesting article about the biomedical applications of halloysite nanotubes (HNTs) reviewing the numerous applications of this clay mineral in biomedicine and nanomedicine, namely, drug delivery, gene delivery, tissue engineering, wound healing, cancer therapy and stem cell isolation, biosensing, and bioimaging. Compared to carbon nanotubes (CNTs), HNTs are much less expensive and have much larger surface area. The lumen diameter of CNT is much smaller than the lumen diameter of HNT; therefore, CNT can only load the smallest molecules, whereas HNTs can uptake biomacromolecules.

The growing scientific interest for HNT in the biomedical field particularly took place on the last decade, including the controlled/sustained release of drugs or bioactive molecules, medical implants, cancer cell isolation, and tissue engineering scaffolds.

Halloysite-based anticancer drug delivery system and antibiotic and antibacterial delivery systems too are being designed and assessed, the HNT drug hybrid carrier with controlled-release behavior. Antitumor drugs, e.g., curcumin, were used for designing powerful carriers based HNT. The interaction of cationic antibiotics such as tetracycline, ciprofloxacin, and amoxicillin with HNT has been assessed, the mechanism of action being dominated by adsorption due to cation exchange.

These various assays and applications are explained by the ability of HNTs to bind with many synthetic and biological molecules due to the mineral large specific surface area and to the positively charged inner tubes surface (Al-OH groups) and negatively charged outer tubes surface (Si-OH and Si-O-Si groups), as well as due to easy dispersion in water or in polar liquids, high biocompatibility, and low cytotoxicity. The two types of inner and outer OH groups can be used as active sites for functionalization and drug loading through modifications. Diverse types and classes of drugs have been loaded onto the inner lumen of HNT. Studies have shown that HNTs are a novel and potential material for gene and anticancer drug delivery in cancer therapy, such as *curcumin* or *adriamycin* (Liu et al. 2016a, b) and for enhanced anticancer efficacy (Long et al. 2017). Satish et al. (2019) report numerous studies where HNTs have been used as nanocontainers or nanocarriers for drug delivery as well as target drug delivery, the drugs being loaded into the lumen or onto the tubes surface.

The use of HNT in gene therapy holds great potential as a clinical treatment for cancer and genetic disorders is still an ongoing exploration which has seen potentially viable results, taking advantage of its biocompatibility and negligible toxicity (Long et al. 2017).

HNT potential anticancer activity, under the form of co-loaded curcumin/triazole-halloysite systems, has been developed and characterized (Riela et al. 2014; and Yang et al. 2016). Curcumin, a naturally active component isolated from the plant Curcuma longa, is characterized by anti-inflammatory, antioxidant, antiproliferative, and anticancer activities (Mock et al. 2015). HNT has been used too as a delivery agent for tissue engineering for bone implants, dental fillings, and tissue scaffolds. For instance, alkaline phosphatase (ALP) has been incorporated into HNT for bone repair, which activity is highly enhanced and promoting biomineralization (Pietraszek et al. 2019; and Liu et al. 2013). Unfortunately, there are only few studies of the role of HNT as bionanocomposites for tissue engineering (Fakhrullin and Lvov 2016).

Currently, there is a tremendous need to make commercial bone cements. Most bone cements include antibiotics added to prevent bacterial infection during surgery. HNT can encapsulate the antibiotics and retard their release up to several weeks, allowing protection against bacterial infection throughout the treatment. Besides, mixing *halloysite* with bone cements, significant increase of mechanical and cell adhesive properties can be obtained leading to product lifetime extension.

Skin-controlled release using transdermal administration, in the case of cosmetic creams and wound-healing scaffolds, seem to be the most promising biomedical applications of HNT (Abdullayev and Lvov 2016).

The HNT properties, such as high mechanical strength, good biocompatibility, and hemostasis action, make HNT compatible for wound-healing applications.

Multiple studies report the use of *halloysite nanotubes* for loading of antibacterial and antiseptic drugs for wound healing and wound dressing applications (Wei et al. 2014; Liu et al. 2014a, b; Sandri et al. 2017; Kurczewska et al. 2017; Shi et al. 2018; and Pavlináková et al. 2018). Inorganic antibacterial materials have several advantages over traditionally used organic agents due to properties such as chemical stability, thermal resistance, user safety, and long-lasting action. Nanoparticles in particular have been utilized in food preservation, safe cosmetics, medical devices, water treatment, etc.

Recent studies on antibacterial activities of clay-based materials are mainly focused on immobilization of inorganic metals such as Ag^+, Cu^{2+}, and Zn^{2+} onto clay minerals (Girase et al. 2011 and Ghorbanpour et al. 2017). The last authors referred to have demonstrated the antibacterial activity of silver-doped nanoclay against bacterial strains of gram-negative *E. coli* and of gram-positive *S. aureus*, utilizing the disc diffusion method. They have prepared a nanocomposite starting with the immersion of montmorillonite, as the nanoclay, into molten $AgNO_3$, and after the ion exchange process, the obtained nanocomposite was adequately washed, sonicated, filtrated, and dried.

Fizir et al. (2018) produced an interesting review on the use of *halloysite nanotubes* in analytical sciences and in drug delivery. The review covers the following topics:

1. The chemical properties of *halloysites*.
2. The effects of alkali and acid etching on the loading capacity and the release behavior of *halloysites.*
3. The use of *halloysite nanotubes* in analytical sciences and drug delivery.
4. Recent trends in the preparation of magnetic HNTs. The authors believe that the researches on *halloysite* in diverse types of drug delivery systems will bring clinically useful drug dosage forms in the future.

Despite the positive and very promising results of the biomedical applications of HNT, Satish et al. (2019) conclude that the major hindrance in the use of HNT is the absence of studies on humans for pharmaceutical applications. On the contrary, HNTs have been successfully tested on animal models, such as in topical cosmetic formulations, skin ointments, antimicrobial sprays, and traditional oral formulations. Another hindrance is the nonbiodegradable behavior of HNT in blood what impedes the injectable administration into living systems.

10.4.1 Biosensors

Biosensors are chemical sensors in which the recognition system uses a biological mechanism to measure the interaction between the analyte and the sensor device, transforming qualitative information into a measurable electrical signal (Chen et al. 2008). There are studies, mentioned by Oliveira et al. (2018) dealing with the use of clays as electrode modifiers or as clay-containing matrices (Navrátilová and Kula 2003; Mousty 2010; Mousty and Prévot 2013; Mousty and Walcarius 2015; and Zhao et al. 2015). However, only few have studied the biomedical applications of clay biosensors or the diversity of biomolecules associated with clay minerals.

Biomolecules immobilized on clay minerals external and/or internal particle surfaces are important to develop biosensors. Oliveira et al. (2018) show a list of biosensors based on clay modifier electrodes and immobilized biomolecules, and in such list *montmorillonite*, *palygorskite*, and *halloysite* are the clay minerals mostly referred to. *Palygorskite* has been proved to be excellent for the development of biosensors, because of its high specific surface area, high biocompatibility, electrocatalytic activity attributed to its high adsorption capacity, and the presence of OH groups on crystals surface. These features allow electron transfer between the electrode and the detected analytes.

Enzymes are the biomolecules most frequently immobilized on clay matrices, enzymatic biosensors being used, for instance, for the detection of glucose, hydrogen peroxide, and phenol. Halloysite is another clay mineral that due to its tubular structure makes it suitable for biomolecules capture and for the development of enzymatic biosensors. Clay minerals have been proved to be suitable materials to stabilize, and even enhance, the biological activity of the biomolecules (Ghadiri et al. 2015).

The development of biosensors based on nanocomposites is of paramount importance, because they proved to be able to detect trace concentrations of the analyte of interest and to ensure the selectivity, sensitivity, and reproducibility of the system (Ramachandran et al. 2016).

10.4.2 Regenerative Medicine/Tissue Engineering

Nanoclays can be used on the development of biomaterials, for instance scaffolds, because they could satisfy the requirements of cells in a three-dimensional support system, or as a delivery vehicle incorporating bioactive compounds (Bramhill et al. 2017).

Hydrogels containing natural polymers, such as chitosan, gelatin, starch, and gellan gum, can act as integrated networks of scaffolds because of the structural similarity of these components and have the potential to regulate cellular responses, notwithstanding their limited ability to support cell adhesion. Such difficulty could be overcome by modification of their structure or by the incorporation of bioactive molecules, such as proteins, peptides, or yet clay minerals (Chrzanowski et al. 2013; and Oliveira et al. 2018).

Certain polymer-clay mineral nanocomposites can positively contribute to scaffolds because of their high porosity and compressive strength, particularly in bone repair (Dawson and Oreff 2013).

Oliveira et al. (2018) report the existence of some reviews dedicated to experimental clay research in regenerative medicine conducted by Dawson and Oreff (2013), Ruiz-Hitzky et al. (2013, 2015), Chrzanowski et al. (2013), and Bramhill et al. (2017), as well as about 140 studies, published during the last 4 years, involving clay minerals (*montmorillonite*, *halloysite*, *palygorskite*, *sepiolite*, and *kaolinite*) interesting for regenerative medicine; and researchers, such as Barua et al. (2014) and Mohd et al. (2016), have examined the cellular response to biominerals.

For Chrzanowski et al. (2013), the synthetic clay mineral named *laponite* is one of the most actively researched materials in the pharmaceutical industry to be used for drug delivery and tissue engineering, in spite of the mechanism of cell attachment being not yet well understood, a situation that should be resolved before clinical applications. *Laponite* is a synthetic 2:1 trioctahedral clay mineral resembling *hectorite*, the natural clay mineral, and it is synthesizing involves the combination of salts of sodium, magnesium, and lithium with sodium silicates at carefully controlled rates and temperature. *Laponite* chemical structural formula is $Na_{0.7}(Si_8Mg_{5.5}Li_{0.3})O_{20}(OH)_4$ (Christidis et al. 2018), and its individual particle shape in the form of disks of high aspect ratio may strongly interact with many types of chemicals, easily functionalized, and readily degraded in the physiological environment giving rise to nontoxic and even bioactive products. When dispersed in water, *laponite* can form a clear thixotropic gel that could be used in potentially important biomedical applications. Recently Tomás et al. (2018) enhance the applications of Laponite® in drug delivery, bioimaging, regenerative medicine, and tissue engineering.

Halloysite nanotubes (HNT) besides being used as drug delivery agents for various kinds of targets it has have found a particular role as delivery agents for tissue engineering, based on some promising researches carried out and disclosed during the past decade. Satish et al. (2019) report that alkaline phosphatase (ALP) was incorporated in HNT for bone repair, HNT acting as a heat sink in the system which increased the thermal stability of the ALP, and it also highly enhanced the activity of ALP, thus promoting the biomineralization process which was studied in vitro using calcium glycerophosphate as the substract. This bioactive nanocomposite can also be incorporated into biomaterials used as scaffolds for tissue engineering. The authors above referred to consider that *scaffolds* need to be competent enough to support the three-dimensional tissue formation. Also, they should meet specific requirements:

1. High porosity with adequate pore size to facilitate seeding and diffusion of nutrients.
2. Biodegradability and degradation rate; the *scaffold* should be absorbed by tissue surrounding it along with the new tissue formation.

3. Mechanical strength for strong support for growth of new tissue.

Chitosan-HNT nanocomposite *scaffolds* show better properties than nanocomposites just based in chitosan. Other studies are being carried out involving sodium-alginate-HNT nanocomposites (Liu et al. 2015; and Huang et al. 2017), chitosan-gelatine-agarose hydrogel doped with HNT (Naumenko et al. 2016), and other hydrogels integrating HNT (Bonifacio et al. 2017, and Fakhrullin and Lvov 2016). Polyethyleneimine-grafted HNTs are being studied as carrier for gene delivery (Long et al. 2017).

Fibrous clay minerals, *palygorskite* and *sepiolite*, compared with layered clay minerals, *montmorillonite*, *kaolinite*, and *halloysite*, show advantages attributed to the high density of silanol groups, which allows hydrogen bonding in addition to Van der Waals forces at the polymer-clay mineral interface (Ruiz-Hitzky et al. 2013).

Besides clay minerals other bioactive nanominerals and nanomaterials, for instance, bioactive ceramics and glasses can be implanted into the body. Bioactive ceramics are implanted into the human body to replace existing parts that have become diseased, damaged, or worn out. More than one million hip prostheses using *alumina* (Al_2O_3) components have been performed. Alumina is a very important bioceramic because it is biocompatible – it does not produce any adverse reactions in the body. One of the disadvantages of alumina, since it is nearly an inert bioceramic, is that it does not allow interfacial bonding with tissues.

The most important bioactive ceramic is *hydroxyapatite* (HA), which is very similar to the mineral making part of teeth and bone composition. HA has been much applied in regenerative medicine, usually in composites with polymers. Unlike alumina HA allows interfacial bonding with the tissues. The biological apatites, which are the mineral phases of bone, enamel, and dentin, are usually referred to as HA (hydroxyapatites). The apatite group of minerals has the general formula $A_{10}(BO_4)_6X_2$. In HA, or more specifically calcium hydroxyapatite, A = Ca, B = P, and X = OH. The mineral part of teeth and bones is made of an apatite similar to HA crystals. Natural bone is ~70% HA by weight and 50% HA by volume. Actually, they differ from pure HA in stoichiometry, composition, and crystallinity, as well as in other physical and mechanical properties. Biological apatites are usually Ca-deficient and are always carbonate substituted, $(CO3)^{2-}$ for $(PO4)^{3-}$. For use in biomedical applications HA is prepared in one of two forms: either dense or porous (Carter and Norton 2007).

10.5 Nanomaterials Toxicity and Regulations

NPs specific properties much dependent on their synthesis methods can pose health negative impacts, i.e., toxicity. It is noteworthy that the chemical composition and shape of the nanoparticles are main factors contributing to nanoparticle toxicity, other than size and aging. Hence, many NPs are nontoxic, while others have reduced toxicity or may also have progressive health effects (Buzea et al. 2007). Nanomaterial toxicity is a matter of increasing concern.

According to Jeevanandam et al. (2018), based on the so far known toxicological data, the toxicity of NMs depends on the effects of various factors, shortly identified as follows:

1. Dose and exposure time effect
2. Aggregation and concentration effect
3. Particle size effect
4. Particle shape effect
5. Surface area effect
6. Crystal structure effect
7. Surface functionalization effect
8. Pre-exposure effect

The factors referred to are reasonably detailed by the aforesaid authors.

High chemical bioactivity and reactivity as well as the ability to penetrate cells, tissues, and organs are properties that make nanomaterials very useful in biomedical applications. However, as Jeevanandam et al. (2018) point out, these merits are also avenues for potential toxicity, the reason why regulations via legislation, laws, and rules have been implemented by several government organizations to avoid or minimized risks associated with NMs. However, there is no specific international regulation neither internationally agreed protocols or legal definitions for production, handling or labeling, testing toxicity, and evaluating the environmental impact of NMs.

Currently, the USA and the EU (European Union) have strong regulatory bodies and guideline legislation to control the potential risks of NMs. About this subject Jeevanandam et al. (2018) provide very interesting information.

References

Abdullayev E (2015) Medical and health applications of halloysite nanotubes. In: Pasbakhsh P, Churchman GJ (eds) Natural mineral nanotubes. Apple Academic Press, Oakville, pp 421–436

Abdullayev E, Lvov Y (2013) Halloysite clay nanotubes as a ceramic skeleton for functional biopolymer composites with sustained drug release. J Mater Chem B1:2894–2903

Abdullayev E, Lvov Y (2016) Halloysite for controllable loading and release. Developments in Clay Science, vol. 7, Chapter 22, Elsevier Ltd, pp 554–605

Aguzzi C, Cerezo P, Viseras C, Caramella C (2006) Use of clays as drug delivery systems: possibilities and limitations. Appl Clay Sci 36:22–36

Aguzzi C, Sandri G, Cerezo P, Carazo E, Viseras C (2016) Health and medical applications of tubular clay minerals. Developments in Clay Science, vol. 7, Chapter 26, Elsevier Ltd, pp 708–725

Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, Kouhi M (2013) Liposomes: Classification, preparation and applications. Nanoscale Res Lett 8(1):102, Springer

Alcântara A, Darder M, Aranda P, Ruiz-Hitzky E (2014) Polysaccharide-fibrous clay bionanocomposites. Appl Clay Sci 96:2–8

Arnold DE (2005) Maya blue and palygorskite a second possible pre-Columbian source. Anc Mesoam 16:51–62. https://doi.org/10.1017/S0956536105050078

Arnold DE, Branden JR, Williams PR, Feinman GM, Brown JP (2008) Antiquity 82:151–164

Bagher AM (2016) Quantum dots applications. Sens Trans 198(3):37–43

Barenholz Y (2012) Doxil® – the first FDA approved nano-drug: lessons learned. J Control Release 160:117–134

Barua S, Dutta N, Karmakar S, Chattopadhyay P, Aidew L, Buragohain A et al (2014) Biocompatible high performance hyperbranched epoxy/clay nanocomposite as an implantable material. Biomed Mater 9:025006

Bate B, Zhao Q, Burns SE (2014) Impact of organic coatings on frictional strength of organically modified clay. J Geotech Geoenviron 140(1):228–236

Bennet D, Kim S (2014) Polymer nanoparticles for smart drug delivery. Chapter 8 of "Applications of Nanotechnology in Drug Delivery". In: Sezer AD (ed) IntechOpen, https://doi.org/10.5772/58422, eBook: ISBN 978-953-51-5756-4

Bolzinger MA, Briançon S, Chevalier Y (2011) Nanoparticles through the skin: managing conflicting results of inorganic and organic particles in cosmetics and pharmaceuticals. Adva Rev John Wiley & Sons, Inc 3:463–478

Bonifacio MA, Gentile P, Ferreira AM et al (2017) Insight into halloysite nanotubes-loaded gellan gum hydrogels for soft tissue engineering applications. Carbohydr Polym 163:280–291

Borm PJA, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K, Schins R, Stone V, Keyling W, Lademan J (2006) The potential risk of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol 3:11

Bramhill J, Ross S, Ross G (2017) Bioactive nanocomposites for tissue repair and regeneration: a review. Int J Environ Res Public Health 14:66

Breakwell IK, Homer J, Lawrence MAM, McWhinnie WR (1995) Studies of organophilic clays: the distribution of quaternary ammonium compounds on claysurfaces and the role of impurities. Polyhedron 14(17–18):2511–2518

Buzea C, Pacheco II, Robbie K (2007) Nanomaterials and nanoparticles: sources and toxicity. Biointerphases 2:17–71

Cabral H, Miyata K, Osada K, Katauka K (2018) Block copolymers micelles in nanomedicine applications. Chem Rev 118:6844–6892

Cagel M, Tesan FC, Bernabeu E, Salgueiro MJ, Zubillaga MB, Moretton MA, Chiappeta DA (2017) Polymeric mixed micelles as nanomedicines: achievements and perspectives. Eur J Pharm Biopharm 113:211–218

Cameron NM, Mitchell ME (eds) (2007) Nanoscale: issues and perspectives for the Nano century. John Wiley, Hoboken, 462pp

Cao G (2004) Nanostructures and Nanomaterials: Synthesis, properties and applications. Imperial College Press, 2nd edn. 596pp

Carter CB, Norton MG (eds) (2007) Ceramic materials: science and engineering. Springer, 716pp, ISBN: 0387462708

Cervini-Silva J, Nieto-Camacho A, Ramirez-Apain MT (2015) The anti-inflammatory properties of different naturally occurring halloysite. In: Pasbakhsh P, Churchman GJ (eds) Natural mineral nanotubes. Apple Academic Press, Oakville, pp 449–459

Chen G-J, Yen M-C, Wang J-M, Lin J-J, Chiu H-C (2008) Layered inorganic/enzyme Nanohybrids with selectivity and structural stability upon interacting with biomolecules. Bioconjug Chem 19:138–144

Choy J-H, Kwak S-Y, Park J-S, Jeong Y-J, Portier J (1999) Intercalative nanohybrids of nucleoside monophosphates and DNA in layered metal hydroxide. J Am Chem Soc 121:1399–1400

Choy J-H, Kwak S-Y, Jeong Y-J, Park J-S (2000) Inorganic layered double hydroxides as nonviral vectors. Angew Chem 39:4041–4045

Choy J-H, Park M, Oh J-M (2006) Bio-nanohybrids based on layered double hydroxide. Curr Nanosci 2:275–281

Choy J-H, Choi S-J, Oh J-M, Park T (2007) Clay minerals and layered double hydroxides for novel biological applications. Appl Clay Sci 36(1–3):122–132

Christidis GE, Aldana C, Chryssikos GD, Gionis V (2018) The nature of laponite: pure hectorite or a mixture of different trioctahedral phases? Fortschr Mineral 8:314. https://doi.org/10.3390/min80803142018

Chrzanowski W, Kim S, Neel E (2013) Biomedical applications of clay. Aust J Chem 66:1315–1322

Churchman GJ, Pasbakhsh P (2015) Current trends in research and application of natural mineral nanotubes. In: Pasbakhsh P, Churchman GJ (eds) Natural mineral nanotubes. Apple Academic Press, Oakville, pp 481–488

Das S, Mitra S, Khurana SMP, Debnath N (2013) Nanomaterials for biomedical applications. Front Life Sci 7(3–4):90–98

Dawson J, Oreff R (2013) Clay: new opportunities for tissue regeneration and biomaterial design. Adv Mater 25:4069–4086

de Paiva LB, Morales AR, Valenzuela Diaz FR (2008) Organoclays: properties, preparation and applications. Appl Clay Sci 42(1–2):8–24

de Sousa Rodrigues LA, Figueiras A, Veiga F, de Freitas RM, Nunes LCC, da Silva Filho EC, da Silva Leite CM (2013) The systems containing clays and clay minerals from modified drug release: a review. Colloids Surf B: Biointerfaces 103:642–651

Detellier C, Schoonheydt RA (2014) From platy kaolinite to nanorolls. Elements 10:201–206

Ding X, Alani AWG, Robinson JR (2002) Extended-release and targeted drug delivery systems. In: Troy DB (ed) Remington: the science and practice of pharmacy, 21th edn, Lippincott Williams & Wilkins, USA, Chapter 47, pp 939–964

Dockery DW, Pope CA, Xu XP, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE (1993) An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753–1759

Du M, Guo B, Jia D (2010) Newly emerging applications of halloysite nanotubes: a review. Polym Int 59:574–522

Duce C, Vecchio Ciprioti S, Ghezzi L, Ierardi V, Tiné MR (2015) Thermal behavior study of pristine and modified halloysite nanotubes: a modern kinetic study. J Therm Anal Calorim 121:1011–1019

Dykman LA, Khlebtsov NG (2011) Gold nanoparticles in biology and medicine: recent advances and prospects. Acta Nat 3(n°2 (9)):34–55

ESF-European Medical Research Councils Report (2004) Nanomedicine European Science Foundation. 48pp

Fakhrullin RF, Lvov YM (2016) Halloysite clay nanotubes for tissue engineering. Nanomedicine 11:2243–2246

Faulk WP, Taylor GM (1971) An Immunocolloid method for the electron microscope. Immunochemistry 8(11):1081–1083

FDA (Federal Drug Administration) (2011) Considering whether an FDA-regulated product involves the application of nanotechnology. https://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

Fizir M, Dramou P, Dahiru NS, Ruya W, Huang T, He H (2018) Halloysite nanotubes in analytical sciences and in drug delivery: a review. Microchim Acta 185:389. https://doi.org/10.1007/s00604-018-2908-1

Gallo L, Piña J, Bucalá V, Ramirez-Rigo MV (2013) Development of a modified-release hydrophilic matrix system of a plant extract based on co-spray-dried powders. Powder Technol 241:252–262

Ghadiri M, Chrzanowski W, Rohanizadeh R (2015) Biomedical applications of cationic clay minerals. Roy Soc Ch 5:29467–29481

Ghezzi L, Spepi A, Agnolucci M, Cristani C, Giovannetti M, Tiné MR, Duce C (2018) Kinetics of release and antibacterial activity of salicylic acid loaded into halloysite nanotubes. Apll Clay Sci 160:88–94

Ghorbanpour M (2016) Amine accessibility and chemical stability of silver SPR chips silanised with APTES via vapour phase deposition method. J Phys Sci 27(1):39

Ghorbanpour M, Mazloumi M, Nouri A, Iotfiman S (2017) Silver-doped nanoclay with antibacterial activity. J Ultrafine Grained Nanostruct Mater 50(2):24–131

Ghosh P, Han G, De M, Kim CK, Rotello VM (2008) Gold nanoparticles in delivery applications. Adv Drug Deliv Rev 60:1307–1315

Gieseking JE (1939) The mechanism of cation exchange in montmorillonite-beidellite-nontronite type of clay minerals. Soil Sci 47:1–13

Girase B, Depan D, Shah JS, Xu W, Misra RDK (2011) Silver-clay nanohybrid structure for effective and diffusion-controlled antimicrobial activity. Mater Sci Eng C 31(8):1759–1766

Goettler L, Lee K, Thakkar H (2007) Layered silicate reinforced polymer nanocomposites: development and applications. Polym Rev 47:291–317

Gong T, Xie J, Liao J, Zhang T, Lin S, Lin Y (2015) Nanomaterials and bone regeneration. Bone Res 3:15029. https://doi.org/10.1038/boneres.2015.29

Grumezescu AM (2019) Biomedical applications of nanoparticles. Elsevier, Amsterdam, 530pp, ISBN 9780128166307

Guimarães L, Enyashin AN, Frenzel J, Heine T, Duarte HA, Seifert G (2007) Imogolite nanotubes: stability, electronic, and mechanical properties. ACS Nano 1(4):362–368. https://doi.org/10.1021/nn700184k

Guimarães L, Pinto YN, Lourenço MP, Duarte HA (2013) Imogolite-like nanotubes: structure, stability, electronic and mechanical properties of the phosphorous and arsenic derivatives. Phys Chem Chem Phys. https://doi.org/10.1039/c3cp44-250k

Guo M, Wang A, Muhammad F et al (2012) Halloysite nanotubes, a multifunctional nanovehicle for anticancer drug delivery. Chin J Chem 30(9):2115–2120

Hanif M, Jabbas F, Sharif S, Abbas G, Farooq A, Aziz M (2016) Halloysite nanotubes as a new drug-delivery system: a review. Clay Miner 51(3):469–478

Hári J, Polyák P, Mester D, Mičušik M, Omastová M, Kállay M, Pukánsky B (2016) Adsorption of an active molecule on the surface of halloysite for controlled release application: interaction, orientation, consequences. Appl Clay Sci 132–133:167–174

He H, Pham-Huy LA, Dramou P, Xiao D, Zuo P, Pham-Huy C (2013a) Carbon nanotubes: applications in pharmacy and medicine. Biomed research international, Hindawi publishing corporation, vol.2013, Article ID 578290, https://doi.org/10.1155/2013/578290

He FJ, Li J, MacGregor GA (2013b) Effect of longer-term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomized trials. BMJ 346:1325

Heinz (2012) Clay minerals for nanocomposites and biotechnology: surface modification, dynamics and responses to stimuli. Clay Miner 47:205–230

Hoshino H, Ito T, Donkai N, Urakawa H, Kajiwara K (1992a) Lyotropic mesophase formation in PVA/imogolite mixture. Polym Bull 29:453–460

Hoshino H, Yamana M, Donkai N, Sinigersky V, Kajiwara K, Miyamoto T, Inagaki H (1992b) Lyotropic mesophase formations of HPC/imogolite mixture. Polym Bull 28(5):607–614

Hsu SH, Wang MC, Lin JJ (2012) Biocompatibility and antimicrobial evaluation of montmorillonite/chitosan nanocomposites. Appl Clay Sci 56:53–62

Huang X, El-Sayed MA (2010) Gold nanoparticles: optical properties and implementations in cancer diagnosis and photothermal therapy. J Adv Res 1:13–28

Huang B, Liu M, Long Z et al (2017) Effects of halloysite nanotubes on physical properties and cytocompatibility of alginate composite hydrogels. Mater Sci Eng C 70:303–310

Hyeon T (2003) Chemical synthesis of magnetic nanoparticles. Chem Commun 8:927–934

ISO/TS 80004-1 (2010) Nanotechnology vocabulary – part 1: core terms. International Organization for Standardization. Geneva, Switzerland. https://www.iso.org/standard/61240.html

Israelachvili JN (2011) Intermolecular and surface forces, 3rd edn. Academic, London

Jeevanandam J, Barthoum A, Chan YS, Dufresne A, Danquah MK (2018) Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol 9:1050–1074

Jin Y, Yendluri R, Chen B, Wang J, Lvov Y (2016) Composite micropartcles of halloysite clay nanotubes bound by calcium carbonate. J Colloid Interface Sci 416:254–260

Kagawa J (2002) Health effects of diesel exhaust emission, a mixture of air pollutants of worldwide concern. J Toxicol 181–182:349–353

Kajivara K, Donkai N, Hiragiy Y, Inagaki H (1986a) Makromol Chem 187:2883

Kajivara K, Donkai N, Fujiyoshi Y, Inagaki H (1986b) Makromol Chem 187:2895

Katti KS, Katti DR, Dash R (2008) Synthesis and characterization of a novel chitosan/montmorillonite/hydroxyapatite nanocomposite for bone tissue engineering. Biomed Mater 3:034122

Keller S, Toebes BJ, Wilson DA (2019) Active, autonomous, and adaptive polymeric particles for biomedical applications. Biomacromolecules 20:1135–1145

Kim J, Kim HS, Lee N, Kim T, Kim H, Yu T, Song IC, Moon WK, Hyeon T (2008) Multifunctional uniform nanoparticles composed of a magnetite nanocrystal core and a mesoporous silica shell for magnetic resonance and fluorescence imaging and for drug delivery. Angew Chem Int Ed 47:8438–8441

Kim MH, Choi G, Elzatahry A, vinu A, Choy YB, Choy J-H (2016) Review of clay-drug hybrid materials for biomedical applications: administration routes. Clay Clay Miner 64(2):115–130

Kittelson DB (2001) Recent measurements of nanoparticle emissions from engines. Meeting on current research on diesel exhaust particles. Tokyo, Japan

Kurczewska J, Pecyna P, Ratajczak M et al (2017) Halloysite nanotubes as carriers of vancomycin in alginate-based wound dressing. Saudi Pharm J 25:911–920

Lagaly G (1981) Characterization of clays by organic compounds. Clay Miner 16:1–21

Lagaly G (1984) Clay-organic interactions. Phylosoph Trans R Soc London 311:315–332

Lagaly G (1994) Layer charge determination by alkylammonium ions. In: Mermut AR (ed) Layer charge characteristics of clays, CMC workshop lectures, vol 6. The Clay Minerals Society, Boulder, pp 1–46

Lagaly G, Ogawa M, Dékány I (2006) Clay mineral organic interactions. Handbook of clay science, Bergaya F, Theng BKG and Lagaly G (editors). Dev Clay Sci 1:309–377

Lee S, Oren AH, Benson CH, Dovantzis K (2012) Organoclays as variably permeable reactive barrier media to manage NAPLs in ground water. J Geotech Geoenviron 138(2):115–127

Letaief S, Detellier C (2013) Kaolinite-polymer nanocomposites. In: Bergaya F, Lagaly G (eds) Developments of clay science, v.5A, handbook of clay science, 2nd edn. Elsevier, Oxford, pp 707–719

Lim EK, Huh YM, Yang J, Lee K, Suh JS, Haam S (2011) pH triggered drug releasing magnetic nanoparticles for cancer therapy guided by molecular imaging by MRI. Adv Mater 23:2436–2442

Liu R, Zhang B, Mei D, Zhang H, Liu J (2011) Adsorption of methyl violet from aqueous solutions by halloysite nanotubes. Desalination 268(1–3):111–116

Liu M, Zhang Y, Wu C, Xiong S, Zhou C (2012) Chitosan/halloysite nanotubes bionanocomposites: structure, mechanical properties and biocompatibility. Inte J Biol Macromol 51:566–575

Liu M, Jia Z, Jia D, Zhou C (2014a) Recent advance in research on halloysite nanotubes-polymer nanocomposite. Prog Polym Sci 39(8):1498–1525

Liu M, Shen Y, Ao P et al (2014b) The improvement of hemostatic and wound healing property of chitosan by halloysite nanotubes. RSC Adv 4:23540–23553

Liu M, He R, Yang R, Long Z, Huang B, Liu Y, Zhou C (2016a) Polysaccharide-halloysite nanotube composites for biomedical applications: a review. Clay Miner 51:457–467

Liu M, Chang Y, Yang J et al (2016b) Functionalized halloysite nanotube by chitosan grafting for drug delivery of curcumin to achieve enhanced anticancer efficacy. J Mater Chem B 4:2253–2263

Long Z, Zhang J, Shen Y et al (2017) Polyethyleneimine grafted short halloysite nanotubes for gene delivery. Mater Sci Eng C 81:224–235

Lun H et al (2014) Natural halloysite nanotubes modified as an aspirin carrier. RSC Adv 4:83

Lvov Y, Abdullayev E (2013) Functional polymer-clay nanotube composites with sustained release of chemical agents. Prog Polym Sci 38:1690–1719

Lvov Y, Price R (2015) Halloysite nanotubes: applications in nanomaterial research. Institute for Micromanufacturing, Louisiana Tech University, Ruston, LA 71272

Lvov Y, Wang W, Zhang L, Fakhrullin R (2016) Halloysite nanotubes for loading and sustained release of functional compounds. Adv Mater 28(6):1227–1250

MacEwan DMC (1948) Complexes of clays with organic compounds. I. Complex formation between montmorillonite and halloysite and certain organic liquids. Trans Faraday Soc 44:349–367

Massaro M, Lazzara G, Milioto S, Noto R, Riela S (2017) Covalently modified halloysite clay nanotubes: synthesis, properties, biological and medical applications. J Mater Chem B5:2867–2882. https://doi.org/10.1039/C7TB90071F

Massaro M, Campofelice A, Colletti CG, Lazzara G, Noto R, Riela S (2018a) Functionalized halloysite nanotubes: efficient carrier systems for antifungine drugs. Appl Clay Sci 160:186–192

Massaro M, Colletti CG, Lazzara G, Riela S (2018b) The use of some clay minerals as natural resources for drug carrier applications. J Funct Biomater 9:58. https://doi.org/10.3390/jfb9040058

Meng N, Zhou NL, Zhang SQ, Shen J (2009) Controlled release and antibacterial activity chlorhexidine acetate intercalated in montmorillonite. Int J Pharm 382:45–49

Mermut AR, Lagaly G (2001) Baseline studies of the clay minerals society source clays: layer-charge determination and characteristics of those minerals containing 2:1 layer. Clay Clay Miner 49:393–397

Mock CD, Jordan BC, Selvam C (2015) Recent advances of curcumin and its analogues in breast cancer prevention and treatment. RSC Adv 5:75575–75588

Mohanpuria P, Rana NK, Yadav SK (2008) Biosynthesis of nanoparticles: technological concepts and future applications. J Nanopart Res 10:507–517

Mohd S, Abdullah M, Amin K (2016) Gellan gum/clay hydrogels for tissue engineering application: mechanical, thermal behavior, cell viability and antibacterial properties. J Bioact Compat Polym 31:1–19

Mousty C (2004) Sensors and biosensors based on clay-modified electrodes – new trends. Appl Clay Sci 27:159–177

Mousty C (2010) Biosensing applications of clay-modified electrodes: a review. Anal Bioanal Chem 396:315–325

Mousty C, Prévot V (2013) Hybrid and biohybrid layered double hydroxides for electrochemical analysis. Anal Bioanal Chem 405:3513–3523

Mousty C, Walcarius A (2015) Electrochemically assisted deposition by local pH tuning: a versatile tool to generate ordered mesoporous silica thin films and layered double hydroxide materials. J Solid State Electrochem 19:1905–1931

Naumenko EA, Guryanov ID, Yendluri R et al (2016) Clay nanotube- biopolymer composite scaffolds for tissue engineering. Nanoscale 8:7257–7271

Navrátilová Z, Kula P (2003) Clay modified electrodes: present applications and prospects. Electroanalysis 15:837–846

Neil A, Xia T, Madler L, Li N (2006) Toxic potential of materials at the nanolevel. Science 311:622–627

Oh J-M, Kwak S-Y, Choy J-H (2006) Intracrystalline structure of DNA molecules stabilized in the layered double hydroxide. J Phys Chem Solids 67:1028–1031

Oliveira KCBF, Meneguin AB, Bertolino LC, Filho ECS, Leite RSA, Eiras C (2018) Immobilization of biomolecules on natural clay minerals for medical applications. International journal of advances in medical. Biotechnology 1(1):31–40

Pasbakhsh P et al (2013) Characterization of properties of various halloysites relevant to their use as nanotubes and microfiber fillers. Appl Clay Sci 74:47–57

Pasbakhsh P, Silva R, Vahedi V, Churchman GJ (2016) Halloysite nanotubes: prospects and challenges of their use as additives and carriers: a focused review. Clay Miner 51(3):479–488

Pavlináková V, Fohlerova Z, Pavlinák D et al (2018) Effect of halloysite nanotube structure on physical, chemical, structural and biological properties of elastic polycaprolactone/gelatin nanofibers for wound healing applications. Mater Sci Eng C 91:94–102

Pierchala MK, Makaremi M, Tan HL, Pushpamalar J, Muniyandy S, Solouk A, Lee SM, Pasbakhsh P (2018) Nanotubes in nanofillers: antibacterial multilayered polylactic acid/halloysite/gentamicin membranes for bone regeneration application. Appl Clay Sci 160:95–105

Pietraszek A, Karevicz A, Widnic M et al (2019) Halloysite-alkaline phosphatase system –a potential bioactive component of scaffold for bone tissue engineering. Colloid Surf B 173:1–8

Price R, Gaber BP, Lvov Y (2001) In-vitro release characteristics of tetracycline HCI, khellin and nicotinamide adenine dinucleotide from halloysite, a cylindrical mineral. J Microencapsul 18:713–722

Ramachandran R, Chen S-M, Kumar G, Gajendran P, Xavier A, Devi N (2016) High electroactive electrode catalysts and highly sensitive electro analytical techniques for hydrogen peroxide detection. Int J Electrochem Sci 11:1247–1270

Riela S, Massaro M, Colletti CG et al (2014) Development and characterization of co-loaded curcumin / triazole-halloysite systems and evaluation of their potential anticancer activity. Int J Pharm 475:613–623

Ruiz-Hitzky E, Darder M, Fernandes F, Wicklein B, Alcântara A, Aranda P (2013) Fibrous clays based bionanocomposites. Prog Polym Sci 38:1392–1414

Ruiz-Hitzky E, Darder M, Alcântara A, Wicklein B, Aranda P (2015) Recent advances on fibrous clay-based nanocomposites. Adv Polym Sci 267:39–86

Sanchéz del Rio M, Picquart M, Haro-Poniatowski E, van Elslande E, Victor Hugo UC (2006) On the Raman spectrum of Maya blue. J Raman Spectrosc 37:1046–1053

Sanchez C, Julián B, Belleville P, Popall M (2005) Applications of hybrid organic-inorganic nanocomposites. J Mater Chem Issue 15:35–36

Sandri G, Aguzzi C, Rossi S et al (2017) Halloysite and chitosan oligosaccharide nanocomposite for wound healing. Acta Biomater 57:216–224

Sarkar B, Xi Y, Megharaj M, Krishnamurti GSR, Bowman M, Rose H, Naidu R (2012) Bioreactive organoclay: a new technology for environmental remediation. Crit RevEnviron Sci Technol 42(5):435–488

Satish S, Tharmavaram M, Rawtani D (2019) Halloysite nanotubes as a nature's boon for biomedical applications. Nanomedicine 6:1–16

SCENIHR report (2005) Opinion on: the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies (September 28–29)

Sharma HD, Reddy KR (2004) Geoenvironmental Engineering: site remediation, waste xontainment, and emerging waste management technologies. John Wiley & Sons Inc

Shi R, Niu Y, Gong M et al (2018) Antimicrobial gelatin-based elastomer nanocomposite membrane loaded with ciprofloxacin and polymyxin B sulfate in halloysite nanotubes for wound dressing. Mater Sci Eng C 87:128–138

Shoeb E, Hefferon K (2019) Future of cancer immunotherapy using plant virus-based nanoparticles. Future Sci OA 5(7):FSO401

Soule NM, Burns SE (2001) Effects of organic cation structure on behavior of organobentonites. J Geotech Geoenviron 127(4):363–370

Steinmetz NF (2013) Viral nanoparticles in drug delivery and imaging. Mol Pharm 10(1):1–2

Stumm W, Morgan JJ (1996) Aquatic chemistry: chemical equilibria and rates in natural waters, 3rd edn. Wiley, New York

Suresh R, Borkar S, Sawant V, Shende V, Dimble S (2010) Nanoclay drug delivery system. International journal of pharmaceutical sciences and. Nanotechnology 3:901–905

Tan D, Yuan P, Annabi-Bergaya F, Liu D, Wang L, Liu H, He H (2014) Loading and in vitro release of ibuprofen in tubular halloysite. Appl Clay Sci 96:50–55

Theng BKG (2012) Formation and properties of clay-polymer complexes. Develop Clay Sci, vol. 4, 2nd edn. Elsevier Science, eBook ISBN: 9780080885278

Tomás H, Alves CS, Rodrigues J (2018) Laponite®: a key nanoplatform for biomedical applications? Nanomedicine, Nanotechnology. Biol Med 14(7):2407–2420

UN (United Nations) (2012) Questions about nanotechnology. https:www.epa.gov/chemical-research/research-nanomaterials

Veerabadran NG et al (2007) Clay nanotubes for encapsulation and sustained release of drugs. Nano 2(2):115–120

Veerabadran NG, Mongayt D, Torchilin V, Price RR, Lyov YM (2009) Organized shells on clay nanotubes for controlled release of macromolecules. Macromol Rapid Commun 30:99–103

Vergaro V, Lyov YM, Leporatti S (2012) Halloysite clay nanotubes for resveratrol delivery to cancer cells. Macromol Biosci 12(9):1265–1271

Viseras C, Aguzzi C, Cerezo P, Bedmar MC (2008) Biopolymer-clay nanocomposites for controlled drug delivery. Mater Sci Technol 24:1020–1026

Viseras C, Cerezo P, Sanchez R, Salcedo I, Aguzzi C (2010) Current challenges in clay minerals for drug delivery. Appl Clay Sci 48:291–295

Viseras C, Aguzzi C, Cerezo P (2015) Medical and Health applications of natural mineral nanotubes. In: Natural mineral nanotubes: properties and Applications, Apple Academic Press/Waretown, Oakville/Hew Jersey, pp 437–448

Viseras C, Carazo E, Borrego-Sanchez A, Garcia-Villén S-ER, Cerezo P, Aguzzi C (2019) Clay minerals in skin drug delivery. Clay Clay Miner. https://doi.org/10.1007/s42860-018-0003-7

Wacker MG (2013) Nanocarriers for intravenous injection – the long hard road to the market. Int J Pharm 457:50–62

Wacker MG (2019) Frontiers in pharmaceutical nanotechnology. Beilstein Journal of Nanotechnology 10:2538–2540

Wang Y, Hu A (2014) Carbon quantum dots: synthesis, properties and applications. J Mater Chem C 2:6921–6939

Wang L, Xing H, Zhang S, Ren Q, Pan L, Zhang K, Bu W, Zheng X, Zhou L, Peng W (2013) A Gd-doped mg-Al-LDH/au nanocomposite for CT/MR bimodal imagings and simultaneous drug delivery. Biomaterials 34:3390–3401

Ward C, De Witt M, Davis EW (2012) Halloysite nanoclay for controlled release applications. Nanomater Biomed 1110:109–138

Wei JC, Yen YT, Su HL, Lin JJ (2011) Inhibition of bacterial growth by the exfoliated clays and observation of physical capturing mechanism. J Phys Chem C 115:18770–18775

Wei W, Minullina R, Abdullayev E et al (2014) Enhanced efficiency of antiseptics with sustained release from clay nanotubes. RSC Adv 4:488–494

Wilson I, Keeling J (2016) Global occurrences, geology and characteristics of tubular halloysite deposits. Clay Miner 51(3):309–324

Yang J-H, Lee S-Y, Han Y-S, Park K-C, Choy J-H (2003) Efficient transdermal penetration and improved stability of L-ascorbic acid encapsulated in an inorganic nanocapsule. Bull Kor Chem Soc 24:499–503

Yang H, Zhang Y, Ouyang J (2016) Physicochemical properties of halloysite. Developments in Clay Science, v 7, chapter 4, pp 67–91

Yendluri R, Otto DP, De Villiers MM, Vinokurov V, Lvov YM (2017) Application of halloysite clay nanotubes as a pharmaceutical excipient. Int J Pharm 521:267–273

Yildiz I, Shukla S, Steinmetz NF (2011) Applications of viral nanoparticles in medicine. Curr Opin Biotechnol 22(6):901–908

Yuan P, Tan D, Bergaya F (2015) Properties and applications of halloysite nanotubes: recent research advances and future prospects. Appl Clay Sci 112–113:75–93

Yuan P, Thill A, Bergaya F (2016) Nanosized tubular clay minerals: halloysite and imogolite. Developments in Clay Science 7

Zhang JA, Zhang Z, Zhang W (2018) Burn ointment for promoting tissue regeneration and skin growth, and preparation method therefor. United Patent Application n° 15/542,420

Zhao L, Zhou C, Wang J, Tong D, Yu W, Wang H (2015) Recent advances in clay mineral-containing nanocomposite hydrogels. Soft Matter 11:9229–9246

Chapter 11
Biominerals and Biomaterials

Celso S. F. Gomes and João B. P. Silva

Abstract Distinction is made between biominerals and true minerals or minerals *strictu* sensu *(s.s.)*, the first formed by the action of biological or cellular activity, the second formed in the natural environment without human intervention. Biominerals are products of a process called biomineralization and are classified into two categories: bio-essential biominerals forming bones and teeth and pathological biominerals forming the so-called calculi or stones in the kidney, vesica, bladder, gallbladder and in joints, the first providing positive physiological effects, the second providing negative physiological effects and health disorders. This chapter describes the great variety of biominerals, their formation, physical and chemical constitution, and function. The so-called ectopic biomineralization is dealt with too. In particular the chemistry and the causes of pathological biominerals formation are enhanced.

11.1 Biominerals

The human body contains the so-called *biominerals*, since they are formed by the action of biological or cellular activity (Skinner 2000, 2005). The quotes in the term *biominerals* are justified because the true minerals are crystalline solids of inorganic origin formed in the natural environment without human intervention, while the *biominerals* being also crystalline solids analogous to the *true minerals* or *minerals s.s.* are produced in the human body exclusively through biological processes.

Biominerals are produced by living organisms for different purposes, such as support of the body, protection of the vital organs, defense against predators, and others. *Biominerals* can be classified on the same framework as minerals, by chemical composition based on the anionic constituents (Giannossi and Summa 2012). Many *biominerals* are actually composites or agglomerates of crystals separated by organic material.

C. S. F. Gomes (✉) · J. B. P. Silva
Department of Geosciences, Researcher of the Research Unit "GeoBioTec",
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt; madeirarochas@netmadeira.com

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_11

Biomineralization is the process by which living organisms produce minerals often to harden or stiffen existing tissues called mineralized tissues. *Biomineralization* is widespread in species belonging to many forms of life, from bacteria to plants and animals, including human beings.

Some books and book chapters have been more or less recently published on the subject of biomineralization, such as:

"Biomineralization: Medical Aspects of Solubility", issued in 2006, Königsberger E and Königsberger L (editors), John Wiley & Sons, Ltd. (publisher).

Biomineralization: From Nature to Application, volume four issued in 2008 of the book series entitled *Metal Ions Life Science*, Sigel A, Sigel H and Sigel RKO (editors), John Wiley & Sons, Ltd. (publisher).

A Review of Pathological Biomineral Analysis Techniques and Classification Schemes, Chap. 7 of the book entitled *An Introduction to the Study of Mineralogy*, Aydinalp C (editor), and IntechOpen (publisher).

Biomineralization Sourcebook: Characterization of Biominerals and Biomimetic Materials issued in 2014, DiMasi E and Gower LB (editors) CRC Press, Taylor & Francis Group (publisher).

Biomineralization: From Molecular and Nano-Structural Analyses to Environmental Science; it is a very comprehensive book edited by Endo et al. (2018).

The editors of the last book referred to emphasize the great diversity of *biominerals* in terms of structure, composition, morphology, and functional role, depending on organisms, and classify the research on biomineralization as interdisciplinary in methodology, ranging from microscopic observation to molecular biology. Very recently Demichelis et al. (2018), based on studies involving *calcium carbonate*, disclose new developments in the understanding of the mechanisms of biomineralization, i.e., of mineral nucleation and growth, through which ions in aqueous environment associate to form increasingly structured particles that eventually transform into the final crystalline or amorphous polymorph in the presence of biological active molecules.

Crystalline organic compounds formed in the human body (e.g., uric acid and cystine) fit into the biomineral concept. But *biominerals* can also occur in many other living things besides man. *Biominerals* can either be deposited inside organisms or in their outer shells, as is the case, for example, of bivalve shells.

Certain *biominerals* have essential physiological effects, such as bones that can act as a support for the body, protection of vital organs, and defense against predators, can have pathological effects, as with so-called stones or *calculi* that occur in the kidneys and in others components of the urinary system and also in the gallbladder. About 50 *biominerals* are already identified in living things. Most organisms produce mineralized tissues in which phosphates and carbonates of calcium and almost amorphous silica participate.

Calcite and *aragonite* that form the shells of oysters and other mollusks are good examples of biominerals. Also, *magnetite* (Fe_3O_4 or FeO, Fe_2O_3) and *greigite* (Fe_3S_4) existing in the so-called magnetotactic bacteria are other examples of *biominerals*. *Magnetotactic bacteria* are a group of gram-negative bacteria capable of responding to magnetic fields due to the presence in the cytoplasm of nanoparticles of magnetic iron (under *magnetite* and *greigite* forms) surrounded by membrane, called magnetosomes (magnetic dipoles) responsible for orientation and migration of magnetotactic bacteria along the lines of the geomagnetic field. Yan et al. (2012) review all information on *magnetotactic bacteria*, *magnetosomes*, and their applications. Recently magnetosomes were used as drug carriers (Sun et al. 2008) and as contrast agents for MRI (Vereda et al. 2009).

In human tissues the mineralization that occurs in them occurs in two types: *physiological* and *pathological*. Effectively according to Skinner (2000), the biominerals can be classified into two groups:

1. *Biominerals bio-essential for some human physiological systems*, such as bones and teeth
2. *Biominerals pathological*, such as "stone" of the kidney and "stone" of the gallbladder, "stones" that cause certain pathologies

11.1.1 Background Data

As mentioned before *biominerals* result from biological or cellular activity. Among the *bio-essential biominerals* are bones and teeth. Among the *pathological biominerals* are so-called calculi or stones formed in the kidney, vesica, bladder, gallbladder, and joints. *Calculi* are called *uroliths* when they are formed in any segment of the urinary tract. The urinary *calculi* disease or the formation of kidney stones is a common though often extremely painful disease.

The physiological mineralization that occurs in bones and teeth mainly involves the formation of *carbonate-hydroxyfluorapatite* crystals $[Ca_{10}(PO_4,CO_3)(OH,F)_2]$, where the CO_3 radical partially replaces the PO_4 radical.

Elliot (2002) and Dove (2010) published interesting papers on *biominerals* based on calcium phosphate and on *skeletal biominerals*, respectively. Also, Combes et al. (2016) disclosed a rather interesting paper on biominerals based on *apatite*.

In biological apatites HPO_4^{2-} and CO_3^{2-} ions can enter the apatite structure replacing PO_4^{3-} ion, the reason why Winand (1961) and Labarthe et al. (1973) propose, respectively, two general chemical formulas for biological apatites:

$Ca_{10-x}(PO_4)_{6-x}(HPO_4)_x\ (HO)_{2-x}$, with $0 \leq x \leq 2$
$Ca_{10-x}(PO_4)_{6-x}(CO_3)_x\ (HO)_{2-x}$, with $0 \leq x \leq 2$

According to Combes et al. (2016), the general chemical formulas of *biological apatites* are best approximated by the simple combination of the two previous chemical formulas taking into account the possible existence.

$Ca_{10-x}(PO_4)_{6-x}(HPO_4 \text{ or } CO_3)_x\ (HO \text{ or } \tfrac{1}{2}\, CO_3)_{2-x}$, with $0 \leq x \leq 2$

Also, Combes et al. (2016) show the mean elemental composition of dried human main hard tissues (bone, dentine, and dental enamel); the nitrogen shown in bone composition enters into the proteins and nonproteins considered to represent the bone organic matrix.

Pathological mineralization has more complex expression in crystallochemical terms than the physiological mineralization involving the formation of *carbonate-hydroxyapatite* and several other *biominerals*. *Carbonate-hydroxyapatite*, which can be classified as mineral and biomineral depending on the mode of formation, is the most ubiquitous pathological biomineral, frequently found in *atherosclerosis*, *nephrocalcinosis*, *chondrocalcinosis*, and other *ectopic calcifications* and also in renal and dental *calculi*. Other types of calcium phosphate, such as *brushite* [$CaHPO_4.2H_2O$] and *whitlockite* [$(Ca,Mg)_3(PO_4)_2$] and *octacalcium phosphate* [$Ca_8H_2(PO_4)$ $6.5H_2O$] may occur in kidney stones. Other *biominerals* bearing calcium in their chemical compostions and still calcium phosphates are the monoclinic and triclinic forms of *pyrophosphate dihydrate* [$Ca_2P_2O_7.2H_2O$] frequently associated with *chondrocalcinosis* or *pseudogout* in the elderly; the monohydrate and dihydrate forms of *calcium oxalate* [$CaC_2O_4.H_2O$] and [$CaC_2O_4.2H_2O$], respectively, are frequently found in *renal calculi*; and *calcium carbonate* [$CaCO_3$] forms, are rare in kidney stones but frequent in calculations of the gallbladder together with *cholesterol* and *calcium bilirubinate*.

The non-calcium phosphate form, called *struvite* of chemical composition [$MgNH_4PO_4.6H_2O$], also frequently identified in renal calculi, is formed during infections. Still other *biominerals* may be found frequently in kidney stones, such as *uric acid* [$C_5H_4N_4O_3$], *uric acid dihydrate* [$C_5H_4N_4O_3.2H_2O$], *monosodium urate* [$C_5H_3N_4NaO_3.H_2O$], and *ammonium acid* [$C_5H_4N_4NH_4O_3$] urate.

The name *lithiasis* is given to the process of calculi formation by the human body, a process of biological calcification. *Lithiasis* is the cause of diseases known since antiquity, and the most important and most frequently occurring *lithiasis* are *biliary lithiasis* and *renal lithiasis*. Other less frequent kinds of *lithiasis* is *urinary lithiasis* and *salivary lithiasis*.

11.1.2 The Bones and Teeth

In humans, the bone is a mineralized tissue of your body composed of ~60–70% calcium phosphate, ~ 20–30% organic material (consisting of proteins and lipids), and ~ 10% water. Calcium phosphate is the biomineral *bioapatite*, whose composition is close to *carbonatehydroxyfluorapatite*, [$Ca_{10}(PO_4,CO_3)(OH,F)_2$]. And the organic component consists of *type I collagen fibrils* covering ~90% of the total content and other non-collagenous macromolecules which make up ~10%.

Type I fibrillar collagen is the largest organic component of bone making up about 90% organic material, the remaining 10% fraction being non-collagenous macromolecules of extremely acidic proteins that are believed to play important roles in the formation and function of bone tissue.

Glimcher (2006) presents an excellent article on the formation, structure, characterization, and mechanisms of biological calcification. Boskey (2007) presents results of recent biochemical studies revealing the controlling factors of the formation and growth of crystals of *bioapatite* and how the alteration of the process of mineralization can cause diseases as is the case of *osteoporosis*. Beniash (2011) treats in an excellent way the understanding of the basic principles of the formation, structure, and functional properties of the *biominerals* in bone tissues.

The bones that are linked together by the joints also shape the body, support the muscles, and protect the internal organs (brain, lungs, heart, etc.). The so-called skeleton is an organized set of bones fundamental to locomotion. The inorganic component of the bone consists mainly of *bioapatite* (about 67% of the total bone composition) that initially deposited on the organic matrix in the form of calcium phosphate is transformed into *hydroxyfluorapatite* that incorporates varying contents of carbonate, strontium, sulfur, magnesium, sodium, and fluorine (3%). Almost all (about 29%) of the organic component of the bone is composed of a calcified intercellular matrix and cells (about 1%). The matrix is comprised of collagen fibers which is a protein. And the cells that manufacture the bone matrix are called osteoblasts, responsible for resorption of bone tissue.

The teeth are also composites consisting of *enamel*, *dentin, root cement*, and *pulp*, the first three being hard biomineral tissues, also formed by *bioapatite*, and the fourth being soft tissue. The *enamel* which is the hardest tissue of the human body and which coats the crown of the tooth is composed of crushed crystals of *bioapatite* (about 96%) and organic matter and water (about 4%). The *dentin* lies beneath the enamel and consists of *bioapatite* (about 70%), *collagen*, and *water* (about 30%). *Root cement* is a bone-like tissue that surrounds the outer surface of the root. The *pulp* is the vascularized tissue that exists inside the tooth, crown, and root.

11.1.3 Calculi or "Stones"

Calcium phosphate *hydroxyapatite*, $Ca_5(PO_4)_3(OH,F)$, enters in the composition of the bones and teeth, but may also occur as pathological deposits in human tissues, such as arteries, tumors, tendons, and patella. Other *biominerals* may occur in the form of calculi or uroliths (usually called "stones") inside the kidney, gallbladder, urethra, and bladder as a result of chemical precipitation when certain chemical elements in the urine reach states of supersaturation as described above.

Renal lithiasis is a common health problem and affects about 10% of the global population. Mineral formation within the body of an organism is called "biomineralization." And "stones" are concretions formed by accretion of precipitate having a structure consisting of layers overlap.

Modifications of diets and the use of *lithotripsy* may be the means for the elimination of "stones." To reduce the risk of formation of calcium-rich "stones," it is recommended to take in a lot of hyposaline water and diets with reduced sodium and protein content.

The so-called stones may exhibit distinct chemical composition, crystalline structure, and morphology. The compositions and structures that can occur in the "stones" are as follows: calcium oxalates, *whewellite* ($CaC_2O_4.H_2O$) and *weddellite* ($CaC_2O_4.2H_2O$, calcium phosphate, *brushite*, $CaHPO_4.2H_2O$, calcium carbonate, c*alcite* ($CaCO_3$), and *amorphous calcium urate*.

Among calcium oxalates *weddellite* is the most frequent form and crystallizes in the tetragonal system. Calcium oxalates are precipitated from acid or a little alkaline urine. Hsu et al. (2020), using synthetic urine, have investigated the effects of various inhibitors, such as magnesium, citrate, hydroxycitrate, chondroitin sulfate, and phytate, on calcium oxalate nucleation. Many inorganic and organic substances, e.g., magnesium, citrate, hydroxycitrate, chondroitin sulfate, phytate, etc., are known to inhibit stone formation, while low urine volume, calcium, oxalate, and urate can promote stone formation. It was found out that inhibition increases in the following order: magnesium < citrate < hydroxycitrate < chondroitin sulfate < phytate. The most effective inhibitors referred to particularly inhibit the formation of *calcium oxalate monohydrate*.

Calcium phosphates are precipitated from alkaline urine, which may originate from plant-rich diets and rich in phosphates but which may also represent a pathological condition. Although rare, crystals of *calcium carbonate*, *calcium sulfate*, *cystine* (amino acid that forms in patients suffering from *cystinuria*), *leucine*, *tyrosine*, *bilirubin*, and *cholesterol* can be identified in urine sediments.

Calcium is involved in all of these compounds; however, another phosphate without calcium, *struvite*, $MgNH_4(PO_4)6H_2O$, may also occur.

"Stone" with distinct composition can be created in different organs of the same host. The structure and shape of said "stone" may be either solid and have a rounded and smooth surface, or pyramidal, or laminated, or branched, or present as aggregates of sand. The fragmentation of "stone" using *lithotripsy* techniques is particularly difficult when the "stones" have a massive and hard structure and are made up of *calcium oxalate*, the fragmentation being easier when the "stones" are made up of *calcium urate*.

"*Stones*" may still occur in the gallbladder, bladder, pancreas, and prostate. The "stones" of the pancreas are mostly composed of calcium carbonate (*calcite*) and ancillary calcium phosphate and are believed to be the result of alterations in normal tissue structures due to cancer or diabetes.

Uroliths result from the chemical precipitation of calcium salts, such as calcium oxalates (*whewellite* and *weddellite*) precipitated from acid urine, amorphous calcium urate, calcium phosphate (precipitate) from alkaline urine, and calcium carbonate (c*alcite*), and can form in the kidney, bladder, and gallbladder. The process of *uroliths* formation is called *lithiasis* or *urolithiasis* which is a biological calcification and occurs essentially in the urinary and biliary tract. In addition to *urinary lithiasis* and *biliary lithiasis*, there are other types of lithiasis located in the bronchi, intestines, pancreas, and prostate.

Calcium oxalate uroliths are, among all types of uroliths, the most difficult to break and eliminate using the so-called lithotripsy machines, because they are brown, harder, denser, and more homogeneous. On the contrary, *calcium phosphate uroliths* vary from creamy white and chalky to buff or brown showing similarities to coral.

There is a medical indication that the formation of renal uroliths is closely related to the functioning of the kidneys. It is the kidneys that eliminate the excess of phosphorus (P) and calcium (Ca), so that in case of chronic kidney disease, it can happen that the calcium retained leads to the formation of uroliths.

Drinking plenty of fluids, especially water, is medically advised to reduce the possibility of uroliths, with the most pronounced color of urine being the expression of insufficient fluid intake. Doctors also advise non-abuse of black tea drink by this being rich in oxalates. In addition to the discomfort caused by renal colic and the morbidity of a significant number of patients, *renal lithiasis* is a cause of significant socioeconomic costs, whether directly related to their treatment or indirectly related to lost working days.

Calcite itself can occur in the form of microcrystals in the shoulder and knee joints and cause limiting and painful situations. *Calcite*, *vaterite*, and *aragonite*, the three polymorphs of calcium carbonate, may still be constituents of *gallstones*, formed out of bile components. As a rule, the central or nucleus of these “stones” consists of *cholesterol microcrystals*, cholesterol empirical formula being ($C_{27}H_{46}O$). *Cholelithiasis* is the presence of one or more calculi (gallstones) in the gallbladder.

In developed countries about 10% of adults and 20% of people over 65 years old have gallstones.

11.1.3.1 Lithiasis Conditioning Factors

The prevalence of *nephrolithiasis* in the world population is about 10%, with important variations in several regions, even in populations with similar degrees of development. In the European continent, prevalence rates of *nephrolithiasis* are reported between 5 and 9% of the population. Dietary, environmental, and genetic variations may justify the differences. Renal lithiasis is a growing reality in developed or developing countries and appears to be related to improved living conditions and nutritional parameters. According to Carretero and Pozo (2007), Galeno in the second century A.D. mentioned some risk factors for the phenomenon of lithiasis and that in the early nineteenth century, it was admitted that diet, geography, climate, race, heredity, chronic disease, age, and sex had an influence on the formation of lithiasis.

Despite the advances that have occurred in the physicochemical identification of urinary and biliary calculi and in the respective elimination, the factors responsible for human lithiasis have not yet been defined, but, admittedly, they are multifactorial:

1. Dietary factors (dietary habits associated with industrialization and economic development, obesity, and diabetes particularly favor *bile lithiasis*).
2. Environmental factors (increase of *renal lithiasis* with hot climate promoting dehydration, varying with geography within the same country; in black Africa, bile lithiasis is rare).
3. Occupation (sedentarism favors lithiasis).

4. Sex (renal lithiasis more frequent in men and biliary lithiasis more frequent in women)
5. Age (lithiasis is more frequent in the elderly).
6. Inherited (family relationship, probably due to common, hereditary, food, environmental factors).
7. Medication (drugs that modify urine pH favor lithiasis, either by precipitation of calcium phosphate at basic pH or by precipitation of uric acid at acidic pH).

Giannossi and Summa (2012) in what concerns the etiologic factors implicated in kidney stone formation classified them in three classes:

1. Factors related to urine composition, supersaturation, presence of promoters, and deficit of inhibitors
2. Factors related to the urinary system morpho-anatomy
3. Factors related to geographic, behavioral and climate, solar radiation, and soil and water quality

11.1.3.2 Types, Composition, and Modes of Urolith Identification

Figure 11.1 shows the diffractogram obtained by X-ray diffractometry (XRD) of a renal urolith consisting of *waddelite* (calcium oxalate). The technique X-ray diffractometry (XRD), when complemented by the X-ray fluorescence spectrometry

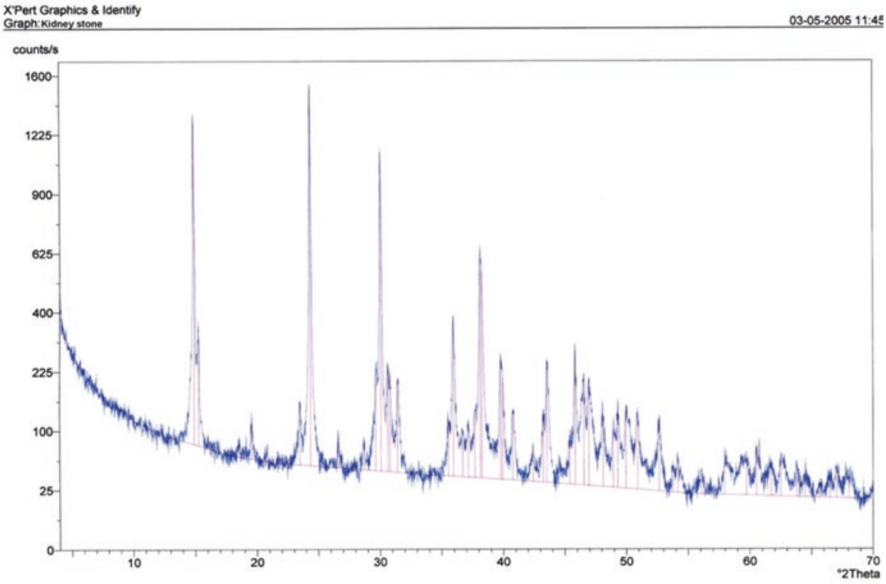


Fig. 11.1 Diffractogram, obtained by X-ray diffractometry, from a renal urolith composed of *waddelite* (calcium oxalate)

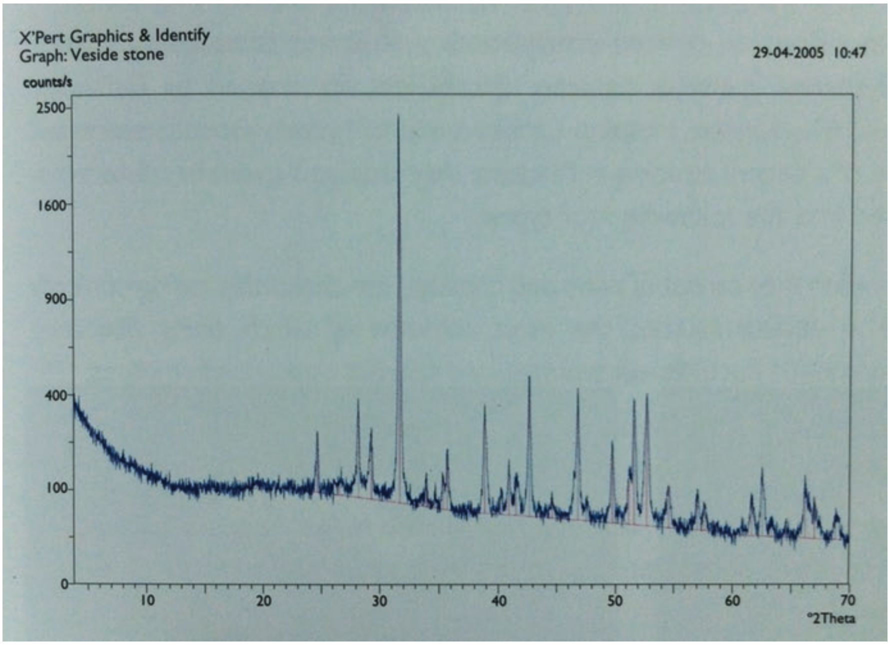


Fig. 11.2 X-ray diffractogram corresponding to a biliary urolith consisting of calcite (calcium carbonate)

(FRX) technique, allows the identification of the crystallochemistry, that is, the organizational structure and chemistry of *uroliths*. Other analytical techniques have been used, such as infrared spectrophotometry, scanning electron microscopy, and microanalysis with electronic probe (Hannache 2014).

Figure 11.2 shows the X-ray diffraction pattern of a *biliary urolith* constituted by *calcite* (calcium carbonate).

11.1.4 Other Biomineralizations

The so-called ectopic calcifications are examples of these other biomineralizations, defined as inappropriate biomineralizations because they occur in the soft tissues and are often associated with tissue alteration and/or necrosis. *Ectopic calcifications* can occur in various parts of the body such as the breast, vascular system, cartilage, prostate, bladder, heart, kidney, liver, and lung and are linked to some important diseases so their detection is essential as well as understanding physicochemical processes associated with their training. An example of *ectopic calcification* is called *mammary microcalcification*. For example, in Europe and the USA, one in ten women will have breast cancer during their lifetime.

If microcalcifications are one of the first indicators of breast cancer, the importance of identifying the chemical nature of microcalcification is recognized today, because while the microcalcification of *calcium phosphate* is often associated with malignant lesions, microcalcification of *calcium oxalate* has been associated to essentially benign lesions. Another type of biomineralization is called *vascular calcification* (VC). *Vascular calcification* (VC), previously considered a passive degenerative condition of aging, is currently characterized as a physiopathological process of active and complexly regulated biomineralization, similar to osteogenesis, that is, bone formation. VC is sometimes found in atherosclerotic lesions and is a common consequence of aging (Jono et al. 2006).

The association between *osteoporosis* (low bone density due to loss of bone mass) and *coronary calcification* or *coronary atherosclerosis* has been reported (Varma et al. 2008; Pierre-Louis et al., 2009). However, a little later, Hajsadeghi et al. (2011) have confirmed this relationship. Also, Beer et al. (2010) had not find a significant relationship between osteoporosis and high limb and myocardial infarction. Elevated levels of serum calcium, *hypercalcemia*, and high phosphorus levels, *hyperphosphatemia*, are indicators of VC.

There is recent news of an innovative diagnostic test that anticipates the heart risk from acute, often fatal, *myocardial infarction*. Cottignoli et al. (2015a) present an important biomineral contribution through morphological and chemical studies of pathological deposits, formed by nanometric crystals of *bioapatite*, in the aortic valves, studies carried out on a significant number of patients of both sexes who underwent the substitution of valves due to severe *stenosis*. Effectively, an electron beam tomography scan allows the detection and quantification of calcium carbonate formations or deposits through the so-called calcium score present in the coronary arteries. The walls of arteries losing elasticity also lose ability to pump blood to the heart. The referred examination allows obtaining an image of the calcification, quantified by the calcium score that occurs inside the coronary arteries.

The mineralization of calcium phosphate, being part of composites constituted by biological matter and mineral matter can produce distinct types of pathologies and occur, for example, in the vascular system of the human body in the form of deposits, the so-called atherosclerotic plaques lining the walls interior of some arteries, as in the case of the thoracic and abdominal aorta. The chemical composition of these mineralizations, which are structurally analogous to *carbonate-hydroxyapatite*, evidences Ca and P as major elements, high CO_3^{2-} content and low H_2O, Cl, F, Mg, Na, K, Si, Zn, Fe, and Pb (Skinner 2000).

Calcific aortic valve stenosis (CAVS) is an important public health problem and represents the most common form of valvular heart disease in the industrialized countries (Rayamannan 2009). It is strictly associated with the formation of ectopic calcifications within aortic valve leaflets that interfere with cusps opening and lead to ventricular outflow obstruction (Akat et al., 2009).

Cottignoli et al. (2015b) have provided new insights into the calcification process by evaluating the spatial relationship existing between bioapatite crystals, their local growing microenvironment. The authors based on analytical data from polarized light microscopy, electron microprobe, scanning and transmission electron microscopy, energy dispersive X-ray spectrometry, powder X-ray diffraction, Fourier transform infrared spectroscopy, and Raman spectroscopy found out that chemically the calcific deposit within human valve tissue is constituted by a non-stoichiometric apatite, containing high carbonate (CO_3^{2-}) content, from 5% to 10% in weight, and AB-type substitutions in apatite lattice, and it is often indicated as "carbonate apatite" or more in general "bioapatite" even if both names are not accepted by the International Mineralogical Association (IMA) Commission on New Minerals, Nomenclature, and Classification (CNMNC).

It is interesting to note that in the venous system, the mineralization does not occur when it would be expected that the blood when it returns to the heart should contain higher concentrations of CO_2 dissolved in the red cells and possibly more HCO_3^- in the serum, an apparently favorable condition for deposition of carbonate apatite. In addition, a possible role of Mg in mineralization is not yet known.

Rapid cell proliferation and death of the cells, being essential conditions for tumor formation, can lead to the formation of calcium phosphate deposits in any tissues of the body. In fact, the genesis of tumors and the deposition of calcium phosphate are interrelated.

According to Skinner (2000), there are as yet no effective chemical methods available for the treatment of apathetic pathological mineralizations which, by virtue of this, are, as a rule, removed by surgery.

Deposits of pathological "minerals" can be formed in the joints producing diseases called gout and arthritis. Crystals of distinctive composition are formed in both synovial fluid and fibrocartilage, *monosodium urate and monohydrate*, $NaC_5H_3N_4O_3.H_2O$; *calcium pyrophosphate,* $Ca_2P_2O_7.2H_2O$; and *hydroxylapatite*, $Ca_5(PO_4)_3(OH,F)$, being the most frequent compositions.

The so-called intra-articular free bodies are also *biominerals* consisting of *hydroxylapatite*.

According to the experts, the intra-articular free bodies can be classified into the following four distinct types:

1. *Osteocartilaginous* - when it consists of bone and cartilage, it is detectable on radiographs and may originate from several sources, the most common being dissecting osteochondritis, osteochondral fractures, osteophytes, and synovial osteochondromatosis.
2. *Cartilaginous* - when loose and radiolucent, it can be traumatic and come from the articular surfaces of the patella and the femoral and tibial condyles.
3. *Fibrous* - when it is also radiotransparent, it is less frequent, and results from hyaline reactions usually originating in the synovium as a consequence of trauma or more often chronic inflammatory processes.
4. *Others* - intra-articular tumors, such as lipomas and localized nodular synovitis, which may give rise to pedicular formations which appear to be free bodies, although they rarely arise and get free.

Figure 11.3 shows an intra-articular body with a nodular and alveolar structure, and Fig. 11.4 shows the corresponding X-ray diffractogram.

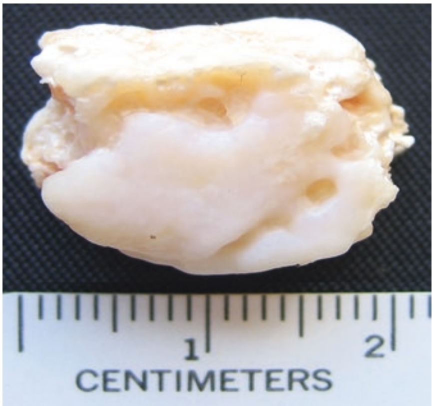


Fig. 11.3 Intra-articular nodule of the *osteocartilaginous type* with a dimension close to 2 cm

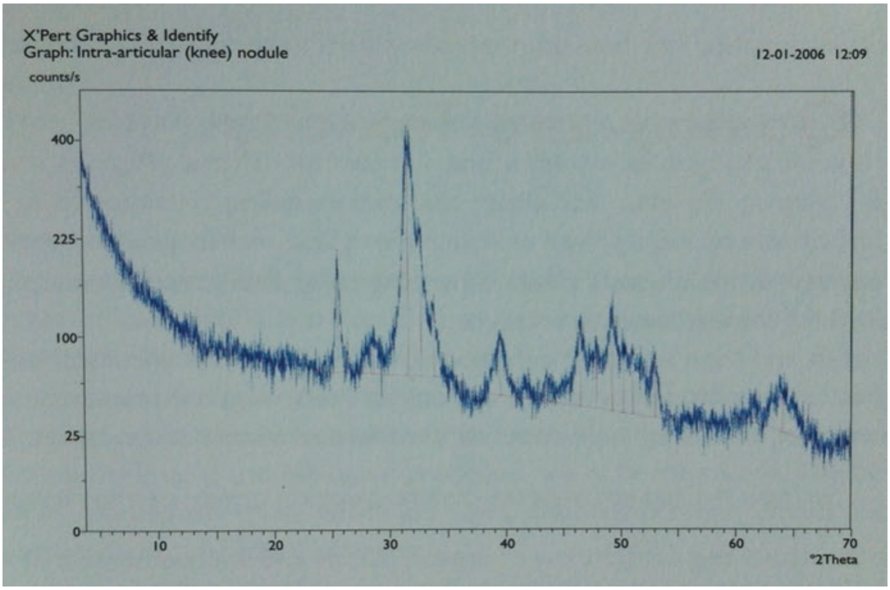


Fig. 11.4 X-ray diffractogram corresponding to the intra-articular nodule shown in Fig. 14.3

The intra-articular body about 2 cm in diameter (kindly assigned for analysis by the orthopedist Dr. Victor Menezes of the Hospital Center of Funchal, Madeira), classified as *osteocartilaginous type*, is constituted by *hydroxyapatite* and was extracted through surgical intervention of the knee of a patient residing on the island of Madeira.

The disease called *gout*, related to abnormal metabolism, is the best known of joint diseases, whose symptoms were already known in Ancient Greece. As a rule, the crystals deposited in the articular areas of patients suffering from gout are composed of *monosodium urate monohydrate*, $NaC_5H_3N_4O_3H_2O$.

Uric acid comes from two types of sources: diet and metabolism of normal cellular systems. The high concentration of uric acid in the blood, called *hyperuricemia* or *hyperuremia*, results in the precipitation of uric acid microcrystals in the tissues and particularly in the joints (elbows, knees, hands, and feet), often affecting the big toe. About 2% of the world's population suffers from gout, first recognized by Hippocrates, much more frequent in men than in women, and is related to overproduction or the deficient elimination of uric acid, an organic compound of the formula $C_5H_4N_4O_3$.

Lifestyle and diet, which can provide hypertension, high cholesterol and triglycerides, diabetes, and obesity, have been recognized as having an influence on gout, a disease that has been attributed to the disease epithet of kings because excess food is high in food and beverages favoring the formation of high concentrations of uric acid was characteristic of the nobility.

Finally, a note for the so-called dental tartar, dental calculus or stone that can form in the teeth, particularly in the interdental spaces, causing oral health problems and aesthetic problems. The *dental tartar* or *dental calculus* begins in the formation of the so-called bacterial plaque, which is a biofilm and which is not cleaned in a timely and convenient manner, hardened by the effect of mineralization or calcification involving the concentration of calcium and phosphorus salts. The final result is the formation of a hard-brown product with 70–90% mineral salts, in particular calcium phosphate, $Ca_3(PO_4)_2$, but also calcium carbonate, $CaCO_3$ (*calcite*), and also an organic component which consists of proteins (~ 6%), carbohydrates (~ 2%), lipids (~ 0.2%), and others (~ 3.8%). The inorganic or mineral component begins with a phosphate near *brushite*, $Ca[HPO_4].2H_2O$, passes to an *octacalcium phosphate*, $Ca_8[HPO_4]_4$, and ends in, $Ca_5[PO_4]_3(OH,F)$ phosphate, where the radical PO_4 can be partially replaced by the radical CO_3.

In 2014 an international team of scientists (Swiss, Americans, English, and Portuguese) even investigated (results published in the journal *Nature Genetics*) the *tartar* glued to the teeth of medieval skeletons dating of 1100 A.D. and coming from the cemetery of the monastery of Dalheim, Germany, revealing for the first time that the tartar already flourished in the human mouth almost thousand years ago.

The *tartar* begins in the bacterial plaque that develops on the surface of the teeth in the lack of oral hygiene, plaque that hardens by mineralization (calcification and) promoted by the chemistry of saliva. This mineralization can preserve and phosphatization capture the biomolecules of all domains of life, that is of a microbiome that preserved in a mineral matrix is very important for those who investigate biological archeology.

Studies have shown that the bacteria that currently cause diseases in the oral cavity are essentially the same as they were around 900 years ago. The "Pompeii microbial" has been found on the teeth of human skeletons, just as volcanic ash as entombed the citizens of the ancient Roman city of Pompeii; the *dental plaque* had preserved bacteria and food particles.

11.1.5 Biomineralization and Biominerals: Research Output

Some books and book chapters have been more or less recently published on the subject of biomineralization and biominerals, such as

Biomineralization: Medical Aspects of Solubility, issued in 2006, Königsberger E and Königsberger L (editors), John Wiley & Sons, Ltd. (publisher).

Biomineralization: From Nature to Application, volume four issued in 2008 of the book series entitled *Metal Ions Life Science*, Sigel A, Sigel H and Sigel RKO (editors), John Wiley & Sons, Ltd. (publisher).

A Review of Pathological Biomineral Analysis Techniques and Classification Schemes, Chap. 7 of the book entitled "An Introduction to the Study of Mineralogy", Aydinalp C (editor), and IntechOpen (publisher).

Biomineralization Sourcebook: Characterization of Biominerals and Biomimetic Materials issued in 2014, DiMasi E and Gower LB (editors) CRC Press, Taylor & Francis Group (publisher).

Biomineralization: From Molecular and Nano-Structural Analyses to Environmental Science; it is a very comprehensive book edited by Endo et al. 2018.

The editors of the last book referred to emphasize the great diversity of *biominerals* in terms of structure, composition, morphology, and functional role, depending on organisms, and classify the research on biomineralization as interdisciplinary in methodology, ranging from microscopic observation to molecular biology. Very recently Demichelis et al. (2018), based on studies involving *calcium carbonate*, disclose new developments in the understanding of the mechanisms of biomineralization, i.e., of mineral nucleation and growth, through which ions in aqueous environment associate to form increasingly structured particles that eventually transform into the final crystalline or amorphous polymorph in the presence of biological active molecules.

11.2 Biomaterials

11.2.1 Definitions, Historical Evolution, and Targets

By definition *Biomaterials* are materials designed to be used in close contact with biological systems, tissues, and fluids and to serve a medical purpose replacing a damaged tissue and organ or treating a disease.

The word "biomaterial" was established in the mid-twentieth century, but *biomaterials* have been used from much earlier (Ratner et al. 2004). Over the years various definitions of biomaterial have been proposed, such as: "A synthetic material used to replace part of a living system or to function in intimate contact with living tissue." Williams 1987 defined "biomaterial" as "A nonviable material used in a medical device intended to interact with biological systems." If the word "medical" is removed in this definition, the concept becomes broader and could encompass a wider range of applications.

The initial use of *biomaterials* for medical purposes dates back as far as 3000 B.C. with the use of linen sutures in Egypt (*nylon* as suture material has just appeared in 1941) and from 600 A.C. with the use of seashells for artificial teeth, as is the case of the Mayan people. The Romans, Chinese, and Aztec have used gold in dentistry more than 2000 years ago.

Early medical implants were rarely successful due to lack of knowledge related to infection control and the *biocompatibility* of the materials. Large wounds were closed early in history by one of two methods: cautery or suture. Metallic sutures using gold wire are first mentioned in early Greek literature by Galen of Pergamon (circa 130–200 A.C.) (*In*: Ratner et al. 2004).

In medicine, "biocompatibility involves the acceptance of an artificial implant by the surrounding tissues and by the body as a whole." Williams 1987 defined "biocompatibility" as the "Ability of a material to perform with an appropriate host response in a specific application."

At the dawn of the twenty-first century, biomaterials are widely used throughout medicine, dentistry, and biotechnology. Just 50 years ago, biomaterials as we think of them today did not exist. The word "biomaterial" was not used. There were no medical device manufacturers, except for external prosthetics such as limbs, fracture fixation devices, glass eyes, and dental devices (*In*: Ratner et al. 2004).

Biomaterials are in wide use, including for *titanium* (Ti) hip implants, microcapsules for drug delivery, and engineered skin. Examples of *biomaterials* include metals (e.g., *titanium*), ceramics, glass, polymers, and even living cells and tissue all can be used in creating a biomaterial. They can be reengineered into molded or machined parts, coatings, fibers, films, foams, and fabrics for use in biomedical products and devices. These *biomaterials* can be found in medical tools such as contact lenses, pacemakers, heart valves, orthopedic devices, and much more.

Biomaterials play an integral role in medicine today, restoring function and facilitating healing for people after injury or disease.

11.2.2 Classes of Biomaterials

Biomaterials may be natural or synthetic and are used in medical applications to support, enhance, or replace damaged tissue or a biological function.

Biomaterials can be classified into three classes:

1. Synthetic (metals, polymers, ceramics, and composites)
2. Nature-derived (e.g., plant-derived and tissue-derived)
3. Semisynthetic or hybrid

Metals and alloys are mostly used for load-bearing applications, such as orthopedic implants (wires, plates, screws, total or partial joint replacements) and dental applications. The metal *titanium*, Ti, for instance, has become the *biomaterial* of choice for facial osteosynthesis. Ti is considered a highly biocompatible and corrosion resistant material, although the ultrastructural behavior of Ti in human tissues after bone fixation is not well documented.

Biopolymers are mainly used for non-load-bearing applications, such as vascular prosthesis, catheters, drug delivery aids, facial prosthesis, skin/cartilages, intraocular prosthesis and in conjunction with metals in orthopedics and dentistry. The modern type of polymeric biomaterials also includes polymeric materials in liquid, film, and gel forms that are used as medical adhesives and sealants, coatings, and fillers.

Bioceramics are refractory polycrystalline compounds that might be *bioinert* (e.g., alumina and zirconia); *bioactive* (e.g., bioglass and high-temperature sintered hydroxyapatite); *biodegradable* (e.g., low-temperature sintered hydroxyapatite and tricalcium phosphate) for dental restorations and artificial joints; and *composites*, a relatively new class of synthetic biomaterials that combine the benefits of its components, such as ceramic/polymer composites used to fill bone cavities as bone cements in dental and orthopedic applications, and they might be synthetic, natural, or a combination of both.

Natural biomaterials are largely composed of three types of biopolymers: proteins, polysaccharides, and polynucleotides. They might be derived from plants, animals, and humans, being identified as facilitators and promoters of healing and specifically used for tissues repair and regeneration (Shin et al. 2003; Lee and Shin 2007).

11.2.3 Tissue Engineering and Regenerative Medicine

Tissue engineering is an interdisciplinary field dedicated to the regeneration of functional human tissues. The classic paradigm relies on a combination of *biomaterial* scaffolds, cells, and bioactive molecules to orchestrate tissue formation and integration within the host environment.

The process of *tissue engineering* is a complicated one. It involves forming a 3D functional tissue to help repair, replace, and regenerate a tissue or an organ in the body. The tissue grows on these scaffolds to mimic the biological process or structure that needs to be replaced.

Three general components are involved in *tissue engineering*:

1. Reparative cells that can form a functional matrix
2. An appropriate scaffold for transplantation and support
3. Bioreactive molecules such as cytokines, and growth factors that will support and choreograph formation of the desired tissue

The goal of *tissue engineering* is to assemble functional constructs that restore, maintain, or improve damaged tissues or whole organs.

Artificial skin and cartilage are examples of engineered tissues that have been approved by the FDA; however, currently they have limited use in human patients.

Body tissues grow by increasing the number of cells that make them up. Cells in many tissues in the body divide and grow very quickly between conception and adulthood. Once we are grown up, many cells mature and become specialized for their particular job in the body and they don't reproduce so often.

Bioprinting covers a broad range of biomaterials. Currently, *bioprinting* can be used to print tissues and organs to help research drugs and pills. However, emerging innovations span from bioprinting of cells or extracellular matrix deposited into a 3D gel layer by layer to produce the desired tissue or organ.

In any machine, the repeated activity of its parts or functional components causes them to deteriorate, so that sometimes their replacement is necessary in order to keep the machine in good working order. The same happens in the human body, repairing the surgeons by using the so-called grafts that are classified into three types: *autografts* (transplantation of organs or tissues from the patient); *allografts* (transplantation of organs or tissues from another patient); and *xenografts* (transplantation of organ or tissue from a donor belonging to a species other than human).

Because of the limited availability of the *most biocompatible* and the *least rejectable autografts*, synthetic materials, generally referred to as biomaterials, have traditionally been designed by the so-called material engineers. Effectively the *biocompatibility* with the tissues with which they interact is the essential requirement of *biomaterials*. These materials may be various: *metal alloys* (used, e.g., in a hip prosthesis), *ceramics* based on *zirconia* (ZrO_2), and *alumina* (Al_2O_3), which being inert or quasi-inert allows the formation of connective tissue at the interface with the connective tissue of the host, and bioactive, for example, some types of glass that allow the establishment of strong bonds to the bone tissue, inducing the formation of new bone. Once again, the interdependence between *minerals* and *humans* is evident, in the present case in terms of health.

One more word for the so-called state-of-the-art biomaterials on the basis of which it is possible to *fabricate* human tissues and organs using the so-called tissue engineering and regenerative medicine. *Regenerative medicine* encompasses a broad category of approaches involving replacement or regeneration of cells, tissues, and organs to restore their natural functions.

The *biomaterials* of last generation possess high porosity and are biodegradable, which function as carriers; it is possible to "sow" cells of different origin and type. If these structures, after being placed in the so-called bioreactors, are subjected to suitable stimuli, the degradation of the support can be achieved as new tissue is being constructed. This will be the basis for future *regenerative medicine* that will replace a diseased organ with a healthy one produced by man.

Among the tissues of the human body, the bone has been the most investigated in tissue engineering due to its high potential for regeneration.

A reference to the Research Group 3Bs (biomaterials, biodegradables, and biomimetics) of the ICVS Associated Laboratory, created in 1998 at the University of Minho and which, since 2008, is part of the European Institute of Excellence in Tissues Engineering and Regenerative Medicine that comprises 22 institutional partners from 13 countries. The Group 3B's develops research in the interfaces of Biotechnology, Biomedical Engineering, and Materials Science, involving objectives such as *Regenerative Medicine*, *Nanomedicine* (drug delivery based on natural polymers), *Isolation and Differentiation of Stem Cells* and *Engineering of Tissues* (bone, cartilage, muscle, and skin).

Regarding the *regenerative medicine* of the bone tissue, we emphasize the recent publication of members of the Group 3B's (Pina et al. 2015).

Very recent information tells that researchers at the University of Louisville, USA, have announced that within 10 years they will be able to create an artificial heart using a 3D printer and living cells from a patient who needs a transplant. The researchers say that a "*bio-impressed or printed*" heart will not have rejection problems because it will be made from the patient's own cells. The construction will involve the creation of five interconnected systems: valves, coronary vessels, microcirculation, contractile cells, and electrical system. Part of this set has already been successfully applied in a mouse.

A project led by the Institute of Molecular Medicine (IMM) of the University of Lisbon, with the collaboration of the University of Aveiro, the Faculty of Engineering of the University of Porto, the University of Edinburgh, the Curie Institute (Paris), and the French company Fluigent, aims to produce within 3 years human muscle in vitro from stem cells, irrigated by blood vessels and innervated with neurons. If the design is successful, the application of artificial muscle may, for example, treat injuries derived from sports practices and also generative losses of muscle mass caused by aging.

Nanosized *cationic clay minerals* can have four major applications in *regenerative medicine*:

1. Enhancing the mechanical properties of polymers
2. Delivering biomolecules
3. Improving cell adhesion
4. Facilitating the proliferation and differentiation of stem cells to bone cells

In all these applications, hybrids made from clay minerals and a variety of biodegradable and biocompatible polymers have been fabricated as 3D scaffolds, hydrogels, and thin films. In tissue engineering, scaffold is a three-dimensional support that is required for initiating cell attachment and for subsequent tissue growth (Salgado et al. 2013). It is also worth mentioning recent advances in the field of bionics, where specialists in Materials Science and Technology, Electronics and Biomedicine seek to build mechanical and electronic devices that can mimic and replace biological functions, devices that incorporate minerals.

With the exception of the brain, the human body can be basically disassembled and rebuilt. Effectively materials such as aluminum and carbon fiber participate in the construction of the skeleton that can be moved by the action of motors and hydraulic systems, and the role of tendons to accumulate and release elastic energy is replaced by the action of springs.

The movement, controlled by a computer, depends on the action of electrical cables that send electrical signals as the nerves would make in a real member. The mechanical nature of the members causes researchers to attempt to construct bionic or robotic replicas of the members. The same is true for certain organs, such as the heart (replaced by a hydraulic pump), pancreas (replaced externally and partially by a computer that monitors blood glucose and administers the correct dose of insulin), and other organs.

A key factor in *biomedical engineering* is the *biocompatibility* between the materials to be used and the biological tissues. For this purpose, the materials must be biologically inert so as not to elicit immune responses.

In the external components of the body, such as the limbs, aluminum, titanium, and carbon fiber are used as structural components, guaranteeing mechanical resistance and flexibility.

Artificial heart valves are often made of metal, such as titanium (Ti) or stainless steel. August 2014 news reports that a medical team at Beijing University in China has replaced a diseased vertebra in a 12-year-old child with a 3D-printed prosthesis made up of overlapping layers of *titanium* (Ti) powders.

The bionics already provided, in the case of the limbs, to build prostheses that exceed human capacities in terms of strength and speed. But the complexity of the internal organs and the way they interact make it difficult to replace them with well-fitted prostheses. It remains the expectation of bionic man to come 1 day to imitate and totally replace the biological functions of the real man. Artificial heart valves are often made of metal, such as *titanium* (Ti) or *stainless steel*.

Biomaterials are synthetic and natural materials that are used in a wide variety of implants, devices, and process equipment that contact biological systems. Millions of lives are saved, and the quality of life is improved for millions more relying on *biomaterials*.

The field of biomaterials that is about some 60–70 years old significantly impacts human health, the economy, and many scientific fields.

Biomaterials and the medical devices comprised of them are now commonly used as *prostheses* in cardiovascular, orthopedic, dental, ophthalmological, and reconstructive surgery and in other interventions such as surgical sutures, bioadhesives, and controlled drug release devices.

The compelling human side to *biomaterials* is that millions of lives have been saved, and the quality of life improved for millions more, based on devices fabricated from biomaterials. The *biomaterial* field has seen accelerating growth since the first medical devices that were based on accepted medical and scientific principles made their way into human usage in the late 1940s and early 1950s. And the growth of the field is ensured, with the aging population, the increasing standard of living in developing countries, and the growing ability to address previously untreatable medical conditions.

The *biomaterials* science is supported by the fundamental studies such as physics, chemistry, and biology, as well as material science. Biomaterials science addresses both therapeutics and diagnostics. It encompasses basic sciences (biology, chemistry, and physics), and engineering and medicine. The translation of biomaterials science to clinically important medical devices is dependent on:

1. Sound engineering design
2. Testing in vitro, in animals and in humans

3. Clinical realities
4. The involvement of industry permitting product development and commercialization

Maintaining the quality of life in an aging population is one of the great challenges of the twenty-first century. This challenge is being met and solved by multidisciplinary contributions and developments of *specialty biomaterials*: devices, artificial tissues and organs, and in vitro growth of human cells as tissue engineered constructs.

Novel *biomaterials*, which might be bioderived, bioinspired, biomimetic, and biocompatible self-healing materials, are now represented in a very wide range of physiologically compatible molecular structures, coatings, membranes, gels, drug delivery carriers, cell culture scaffolds, as well as multi-functional *biomaterials*. The innovations in *biomaterials* include the development of improved structural *biomaterials* such as novelty metals and lightweight alloys, biodegradable metals, ceramic or polymeric materials, as well as materials with special surface modifications, to reduce their degradation in body fluids, to improve their performance with respect to tissue integration, or to prevent device-related complications.

One of the mostly researched biomaterials used in various fields of medicine is natural polymer-collagen. Collagen is the most abundant protein in the body (skin, bones, teeth, tendons, cartilage, basement membrane, cornea, etc.). It can be used by different processing techniques in large various molecular structures (micro and nanostructures) as powder, injectable solutions, films, membrane, and matrices (sponges). The use of collagen as biomaterial, biocompatible, and bioresorbable for the connective tissues prosthesis in which collagen is the basic protein is very well-known.

To use collagen as scaffold in the recovery of bone tissue modifications in the structure and composition of matrix, we need to obtain osteoinductive and osteoconductive effect. This can be achieved by the formation of biocomposites with SiO_2, TiO_2, clay, hydroxyapatite, etc. (Vuluga et al. 2012). Clay mineral-based composite improves the thermal and mechanical properties of collagen and has a biostimulative effect on cellular metabolism. The structure of the clay mineral would be like the structure of the living tissue because of the ionic exchange properties in aqueous medium just like the physiological phenomena in the human body where permanent information exchanges are present.

Silicates surface can be modified with different bioactive substances and obtained nanohybrids can be dispersed in a collagen matrix (Potarniche et al. 2011). Depending on the concentration and the method of the silicate incorporation in the collagen protein, nanostructured systems with different morphologies, capable to control release of active principles (antibiotics, anti-inflammatory, enzymes, etc.), can be obtained. These types of nanocomposites can be used in regenerative medicine of bone tissue.

The earliest successful implants, as well as a large fraction of modern ones, were in the skeletal system. Bone plates were introduced in the early 1900s to aid in the fixation of long bone fractures. The development of new materials for the effective repair of bones is an important objective of *biomaterials*. The bone is itself a composite material made up of 60%–70% inorganic mineral crystal, the major component being *hydroxyapatite*, HA, in the form of tiny elongated crystals, and 30%–40% organic matrix, consisting mostly of collagen protein fibers. *Hydroxyapatite*, HA, the synthetic version of bone apatite is one of the most important biomaterials in the bone tissue engineering field. Recently the combination of HA with *chitosan* (CTS), which has excellent biocompatibility, has made those two materials most important for this application. HA of chemical formula, $Ca_{10}(PO_4)_6(OH)_2$, has been extensively used for hard tissue replacement and augmentation due to its biocompatibility and osteoconductive potential. However, this material is difficult to shape into the specific forms required for bone substitution due to its hardness and brittleness.

Combining biopolymers with minerals to give *biomaterials* with the toughness and flexibility of the biopolymer component and the strength and hardness of the mineral filler has its origin in nature, for example, snail and crab shells. Inspired by this, composites of HA and bioorganic polymers that mimic these natural combinations have ignited great interest.

Currently, HA has attracted much attention due to the prospects for its use in the hyperthermic treatment of cancer. To this end, a number of synthetic biocompatible magnetic composites made from HA and magnetic fillers have been developed, for example, spinel ferrites, metallic iron, and hexagonal ferrites.

Brushite ($CaHPO_4 \cdot 2H_2O$)-forming calcium phosphate bone cements have the advantage of being reabsorbable, whereas HA-forming cements are not but suffer from their fast, water-consuming setting reaction, and low mechanical strength.

Traditional implants generally consist of nondegradable materials such as polymer or titanium.

3D printing bone implants have two important benefits: low likelihood of infections and post-surgery complications. Very recently Particle3D, a Danish startup company, is pioneering a novel method for 3D printing lightweight, customized bone implants that fuse with your skeleton before slowly disappearing. Particle3D uses a “bio-ink” made from tricalcium phosphate (TCP) powder particles and fatty acids. TCP been used in reconstructive surgery for decades but is normally manually sculpted by surgeons from solid blocks into the desired implant shape. This approach can limit the potential positive effects of TCP, for example, when it comes to stimulating natural bone growth. Particle3D process most often starts with scans of a patient’s bones or the area where the implant will be placed. The data is fed into a computer program, which allows surgeons and staff to optimize the implant design using CAD computer models. A customized implant is then printed by Particle3D and sent to a hospital for insertion.

3D printing TCP enables the company to create more porous implants. The porous structures allow the implants to function as scaffolds for blood vessels and natural bone to grow, and the implants degrade over time as they are supplanted by natural bone. Trials on pigs and mice have shown new bone marrow and blood vessels developing in the implants after as little as 8 weeks. Particle3D implants can also store medicine within their porous material for much longer than traditional implants can.

11.2.4 Biomaterials: Research Output

A final reference is due to the great development of biomaterials science, particularly in the present century the output being well expressed in a quite significant number of specialized scientific journals and text books, in the last case some being exemplified as follows:

Biomaterials: Principles and Applications issued in 2003 and edited by Park JB and Bronzino JD. CRC Press

Biomaterials Science: An Introduction to Materials in Medicine, 2nd edition issued in 2004, and edited by Ratner BD, Hoffman AS, Schoen FJ, and Lemons JE, Elsevier

Introduction to Biomaterials, 2nd edition issued in 2005 and edited by Enderle J, Bronzino JD, and Blanchard SM. Elsevier/Academic Press

Biomaterials, Artificial Organs and Tissue Engineering, issued in 2005 and edited by Hench LL and Jones JR. Elsevier Ltd

An Introduction to Biomaterials, issued in 2006 and edited by Guelcher SA and Hollinger JO, The Biomedical engineering Series, Neuman MR (editor), CRC Press

Biomaterials: The Intersection of Biology and Materials Science, 1st edition issue in 2008, Tenenoff JS and Mikos AG being the authors, 512 pp. Pearson

Biomaterials Science: An Introduction to Materials in Medicine, 3rd edition issued in 2013, and edited by Ratner BD, Hoffman AS, Schoen FJ, and Lemons JE, Elsevier

Nanobiomaterials: Development and Application, issued in 2013, and edited by Yi DK and Apaefthymiru GC, CRC Press

Principles of Tissue Engineering, fourth edition issued in 2014, and edited by Lanza R, Langer R, and Vacanti J. Elsevier/Academic Press

Advanced Biomaterials and Biodevices, issued in 2014, and edited by Tiwari A and Nordin AN, Advanced Materials Series, Wiley

Regenerative Engineering of Musculosketetal Tissues and Interfaces, issued in 2015, and edited by Nukavarapu SP, Freeman JW, and Laurencin CT. Elsevier Ltd

Regulatory Affairs for Biomaterials and Medical Devices issued in 2015, and edited by Amato SF, Ezzaell RM. Woodhead Publishing Series in Biomaterials, n° 79, WP/Woodhead Publishing

Biomaterials Science and Tissue Engineering: Principles and Methods, issued in 2017, and edited by Basu B, Cambridge IISc. Series

Biomaterials Science: An Introduction to Materials in Medicine, 4th edition issued in 2020, and edited by Wagner W, Sakiyama-Elbert S, Zhang G, Yaszemski M. Elsevier/Academic Press

The last book referred to is the most comprehensive text on biomaterials science, from principles to applications, particularly applications of biomaterials in medicine. Also, about two tens of specialized scientific journals show the output of the new trends and developments on biomaterials.

References

Akat K, Borggrefe M, Kaden JJ (2009) Aortic valve calcification: basic science to clinical practice. Heart 95(8):616–623

Beer S, Saely CH, Hoefle G, rein P, Vonbank A, Breuss J, Gaensbacher B, Muendlein A, Drexel H (2010) Low bone mineral density is not associated with angiographically determined coronary atherosclerosis in men. Osteoporos Int 21:1695–1701

Beniash E (2011) Biominerals-hierarchical nanocomposites: the example of bone. Rev Nanomed Nanobiotechnol 3(1):47–69

Boskey AL (2007) Mineralization of bones and teeth. Elements 3:385–391

Carretero I, Pozo M (2007) Mineralogia Aplicada: Salud y Medio Ambiente. Thomson (editor), Madrid, 406pp

Combes C, Cazalbon S, Rey C (2016) Apatite biominerals. Minerals 6(2):34. https://doi.org/10.3390/min6020034

Cottignoli V, Cavarretta E, Salvador L, Valfré C, Maras A (2015a) Morphological and chemical study of pathological deposits in human aortic and mitral valve stenosis: a biomineralogical contribution. Pathology Research International 15, Article ID 342984, 14pp

Cottignoli V, Cavarretta E, Salvador L, Valfré C, Maras A (2015b) Biological Niches within Human CalcifiedAortic Valves: towards Understanding of the Pathological Biomineralization Process. Hindawi Publishing Corporation BioMed Research International Volume 2015, Article ID 542687, 10 pages https://doi.org/10.1155/2015/542687

Demichelis R, Schuitemaker A, Garcia NA, Koziara K, De La Pierre M, Raiteri P, Gale JD (2018) Simulation of crystallization of biominerals. Annu Rev Mater Res 48:327–352

Dove PM (2010) The rise of skeletal biominerals. Elements 6(1):37–42

Elliot JC (2002) Calcium phosphate biominerals. Rev Mineral Geochem 48(1):427–453

Endo K, Kogure T, Nagasawa H (2018) Biomineralization: from molecular and Nano-structural analyses to environmental science. Springer Open, Springer Nature Singapore Pte Ltd. ISBN: 978-981-13-1001-0

Giannossi ML, Summa V (2012) A Review of Pathological Biomineral Analysis Techniques and Classification Schemes. Chapter 7 of the book “An Introduction to the Study of Mineralogy”, Aydinalp C (editor), IntechOpen

Glimcher MJ (2006) Bone: nature of the calcium phosphate crystals and cellular, structural, and physical chemical mechanisms in their formation. In Medical Mineralogy and Geochemistry, Sahai N & Schoonen (eds), Reviews in mineralogy & geochemistry, vol 64, pp 223–282. Geochemical Society & Mineralogical Society of America

Hajsadeghi S, Khamseh M-E, Larijani B, Abedin B, Vakili-Zarch A, Meysamie A-P, Yazdanpanah F (2011) Bone mineral density and coronary atherosclerosis. J Saudi Heart Assoc 23:143–146

Hannache B (2014) La tithiase urinaire: epidemiologie, rôle des elements traces et des plantes médicinales. Thèse de Doctorat, Université Paris-Sud 11

Hsu Y-C, Ln Y-H, Shiau L-D (2020) Effects of various inhibitors on the nucleation of calcium oxalate in synthetic urine. Crystals 10:333. https://doi.org/10.3390/cryst10040333

Jono S, Shioi A, Ikari Y, Nishizawa Y (2006) Vascular calcification in chronic kidney disease. J Bone Minr Metab 24(2):176–181

Labarthe JC, Bonel G, Montel G (1973) Structure and properties of B-type phosphocalcium carbonate apatites. Ann Chim 8:289–301

Lee SH, Shin H (2007) Matrices and scaffolds for delivery of bioactive molecules in bone and cartilage tissue engineering. Adva Dry Deliv Rev 59(4–5):339–359

Pierre-Louis B, Aronow WS, Yoon JH, Ahn C, Deluca AJ (2009) Relation of bone mineral density to stress test-induced myocardial ischemia. Am J Cardiol 104(2):199–201

Pina S, Oliveira JM, Reis RL (2015) Natural-based nanocomposites for bone tissue engineering and regenerative medicine: a review. Advanced materials. Willey-VCH Verlag, Weinheim, pp 1–27

Potarniche CG, Vuluga Z, Donescu D, Christiansen JdeC, Eugeniu V, Radovici C, Serban S, Ghiurea M, Somoghi R, Beckmann S (2011) Morphology study of layered Silicate/Chitosan nanohybrids. Surface and Interface Analysis, (May 2011), Early View, Online Version, ISSN 1096-9918

Ratner BD, Hoffman AS, Schoen FJ, Lemons JE (2004) Biomaterials science: an introduction to materials in medicine, 2nd edn. Elsevier, Amsterdam

Rayamannan NM (2009) Calcific aortic stenosis: lessons learned from experimental and clinical studies. Arterioscler Thromb Vasc Biol 29:162–168

Salgado AJ, Oliveira JM, Martins A, Teixeira FG, Silva NA, Neves NM, Sousa N, Reis RL (2013) In: Stefano Geuna IPPT, Bruno B (ed) International review of neurobiology, Academic, vol. 108, pp 1–33

Shin H, Seongbong JO, Mikos AG (2003) Biomimetic biomaterials for tissue engineering. Biomaterials 24(24):4353–4364

Skinner HCW (2000) Minerals and human health. In: Vaughan J, Wogelius RA (eds) EMU notes in mineralogy 2, environmental mineralogy. Eotvos University Press, Budapest, pp 383–412

Skinner HCW (2005) Biominerals. Mineral Mag 69(5):621–641

Sun JB, Duan JH, Dai SL, Ren J, Guo L, Jiang W (2008) Preparation and anti-tumor efficiency evaluation of doxorubicin loaded bacterial magnetosomes: magnetic nanoparticles as drug carriers isolated from *Magnetospirillum gryphiswaldense*. Biotechnol Bioeng 101(6):1313–1320

Varma R, Aronow WS, basis Y, Singh T, Kalapatapu K, Weiss MB, Pucillo AL, Monsen CE (2008) relation of bone mineral density to frequency of coronary heart disease. Am J Cardiol 101, 1103–1104

Vereda F, Vicente J, Hidalgo-Álvarez R (2009) Physical properties of elongated magnetic particles: magnetization and friction coefficient anisotropies. Chem Europe, 10(8), 1165–1179

Vuluga Z, Sanporean C-G, Albu MG, Trandafir V, Iordachescu D, Vaside E (2012) Collagen-Modified Layered Silicate Biomaterials for Regenerative Medicine of bone Tissue. Chapter 6 *In*: "Materials Science and Technology"

William DF (1987) Definitions in Biomaterials. Progress in Biomedical Engineering 4, 72pp. Elsevier, Amsterdam

Winand L (1961) Étude physic-chimique du phosphate tricalcique hydraté et de l´‘hydroxyapatite. Ann Chim 6:951–967

Yan L, Zhang S, Chen P, Liu H, Yin H, Li H (2012) Magnetotatic bacteria, magnetosomes and their applications. Microbiological Research, Elsevier 167:507–519

Chapter 12
Psammotherapy or Arenotherapy

Celso S. F. Gomes and João B. P. Silva

Abstract Psammotherapy or arenotherapy or yet sand-bathing is a traditional practice in some countries which have appropriate natural mineral resources for that. This chapter reports examples of sand-bathing based on three distinctive types of sand: biogenic carbonate sand, radioactive monazite-rich sand, and volcanic basaltic black sand. Attempts are recorded in order to scientifically explain the therapeutic effects of these traditional practices, particularly those involving the biogenic carbonate sand in Porto Santo, Madeira Archipelago, Portugal, and the radioactive monazite-rich sand in Guarapari, Vitória do Espírito Santo, Brazil. In the particular case of Porto Santo, the methodologies employed in sand-bathing, which can be taken either in the natural environment (in the transition zone beach/frontal dune) or inside the facilities of spas, for the treatment of musculoskeletal disorders are described and interpreted.

12.1 Background Data

Some special sands are being used worldwide in a therapeutic application called *psammotherapy*, particularly for the treatment of musculoskeletal diseases, under the form of sand-bath. The word *psammotherapy* comes from the word *psammos*, which is the Greek word for sand, and its origins date back thousands of years ago to Ancient Egypt. The Egyptians took "baths" in the hot desert sand, which was naturally heated by the sun's rays, to treat a number of ailments, from scoliosis to inflammatory diseases.

According to Federicci (1980), when marine sand is used as a therapeutic agent, it provides tonicity to the muscular and the locomotor systems. The author says that a sand-bath or psammotherapy is a 10–20 min application of a layer of sand, extracted from the beach down to depths not higher than 30 cm. Also, the author attributes its therapeutic action to the thermal capacity of the sand.

C. S. F. Gomes (✉) · J. B. P. Silva
Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt; madeirarochas@netmadeira.com

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_12

Murgia (1980) demonstrated the efficacy of psammotherapy with the production of endogenous corticoids, the increase of glucose content, the decrease of eosinophils, and the increase of the secretion of urinary testoroids.

As a rule, natural sand is composed of fine grains interspersed with air and moisture. Being a porous system, it is characterized by low heat conductivity. Therefore, the sand system is able to release the heat absorbed from the sun's rays without causing burns, in spite of its high thermal gradient.

However essentially on an empirical basis, psammotherapy has been used for the treatment of the following diseases: osteoarthritis, post-traumatic conditions (fractures, sprains, etc.), extra-articular rheumatism, inflammatory rheumatism, and fibromyalgia.

Psammotherapy is a worldwide practice, well represented by three distinctive examples:

1. Sand-baths with the biogenic carbonate sand occurring on the beaches of Porto Santo' island, archipelago of Madeira
2. Sand-baths with the radioactive sand occurring on the beaches of Guarapari, State of Espírito Santo, Brazil
3. Sand-baths with the dark volcanic sand occurring in the thermal centers of Beppu and Ibusuki, Kyushu Island, Japan, which are naturally warmed by geothermal heat

For more than 200 years, traditional sand-bathing is being practiced in Porto Santo Island, Madeira Archipelago, to treat musculoskeletal disorders. Also, for more than 300 years, Japanese have traveled to Ibusuki's shoreline in search of a sandy cure for rheumatism, back pain, post-stroke paralysis, hemorrhoids, asthma, diabetes, menstrual disorder, infertility, anemia, constipation, obesity, and all sorts of other things the warm sand (50–55°C) is said to cure. This healing power lured both ordinary Japanese and historical figures like Shimazu Nariakira, a powerful daimyo (feudal lord) who built a manor house on the edge of one of the hot springs nearby Ibusuki City.

12.2 Bathing in the Biogenic Carbonate Sands of Porto Santo Island

Biogenic carbonate sands, similar in composition to those occurring in Porto Santo Island of the Madeira Archipelago, also occur in other islands of the Atlantic Ocean: in the archipelago of the Azores, the islands of Santa Maria and Terceira; in the archipelago of the Canary Islands, the islands of Gran Canaria, Fuerteventura, and Lanzarote; and in the archipelago of Cape Verde, the islands of Sal, São Vicente, and Boa Vista. All the archipelagos referred to are part of the biogeographic archipelago of Macaronesia. However, only in Porto Santo the biogenic carbonate sands have been traditionally used for therapeutic purposes, under the form of sand-baths.

Porto Santo is a small Atlantic island of volcanic origin with a total area estimated at 42.2 km^2 (10 km long by 4 km wide, approximately), which is part of the archipelago of Madeira, located to the west of southern Europe, between the coasts of Portugal and Morocco, and between the archipelagos of the Azores and the Canary Islands. The source of the biogenic carbonate sand that occurs on the beaches and dunes of the island was a barrier reef that had been developed, during the Late Pleistocene, on the shallow north-western coastal shelf of the island. The reef was mostly constituted by calcareous algae, symbiotically associated to corals and other organisms. The fragmentation of the calcareous exoskeletons from the organisms making the bioherm (ancient organic reef of moundlike form) was promoted by the abrasion produced by strong sea waves, as seawater level continuously lowered during the Last Great Glaciation (LGG) and the reef became gradually exposed. At the latitude of Porto Santo, when the maximum LGG was reached, about 20,000 years ago, the mean seawater level had lowered a little over 100 m.

Associated to the yellowish-brownish grains of calcium carbonate, a small amount of dark lithic grains (most of them magnetic) occurs, on average not higher than 2% in the sand from beaches and less than 1% in the sand from dunes. The lithic grains are derived from the erosion of the volcanic rocks (basalt, trachyte, and tephra) of Porto Santo.

Effectively for about 200 years, on the island of Porto Santo, the so-called sand-baths were empirically taken on the excellent beach on the south coast (Fig. 12.1),

Fig. 12.1 View of the beach of Porto Santo Island south coast where the traditional sand-baths are taken

more precisely in the transition zone to the frontal dune where sand is dry. Particularly rheumatic disorders such as osteoarthrosis, osteoporosis, fibromyalgia, etc., have been treated with recognized success. Since 1995, studies have been carried out in order to find justifications for such practices.

Sand of fine granularity (grain size less than 0.250 mm and grain tabular habit) was classified as biogenic carbonate sand. The sand is constituted by bioclasts, essentially of calcareous algae, composed mainly of calcite and magnesian calcite, minorly by aragonite, and also by volcanoclasts (tuff, rhyolite, basalt, and magnetite grains) in a much smaller number. The volcanoclastic component of the sand, as a rule, is not more than 10%, and the content of magnetite varies within the range 1–5%.

Datation of the biogenic carbonate sand, using the radiocarbon method, provided ages within the range 15,000–31,000 years BP (Before Present); the sand formation has taken place during the Last Great Glaciation when the barrier reef of coral and calcareous algae existing around the island due to sea level lowering became progressively exposed to sea abrasion and disintegration.

Figure 12.2 shows the overall minerals identified using XRD (X-ray diffraction) in the biogenic carbonate sand.

Figure 12.3a, b shows the microscopic observation fields of a representative sample of the biogenic carbonate sand of Porto Santo Island, the yellow and white grains being *calcite* and *aragonite* and the black grains being *magnetite*.

Figure 12.3c, d shows some bioclasts of the Porto Santo carbonate sand showing significant porosity, which in our opinion should contribute to explain the singular

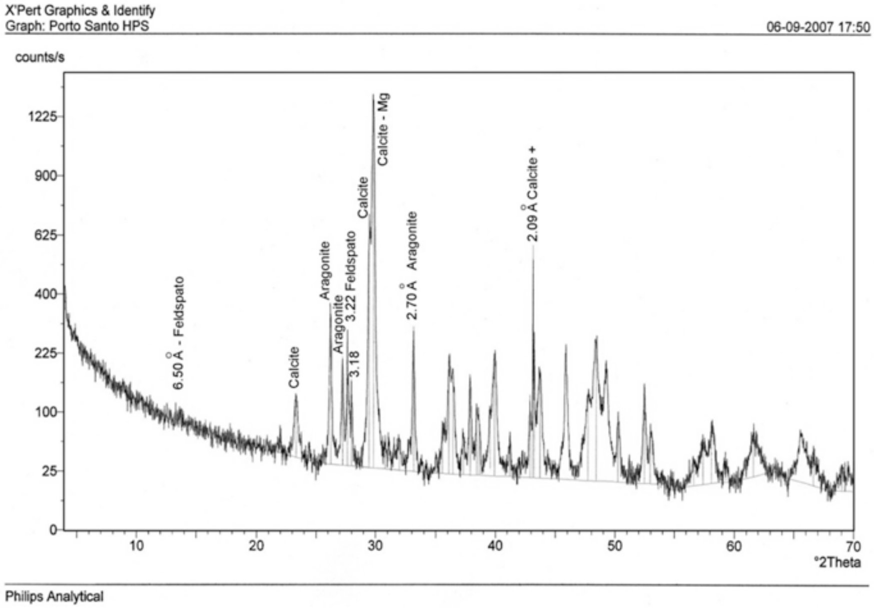


Fig. 12.2 X-ray diffraction pattern of bioclasts of biogenic carbonate sand from Porto Santo Island showing the existence of three carbonate minerals: aragonite, calcite, and magnesian calcite

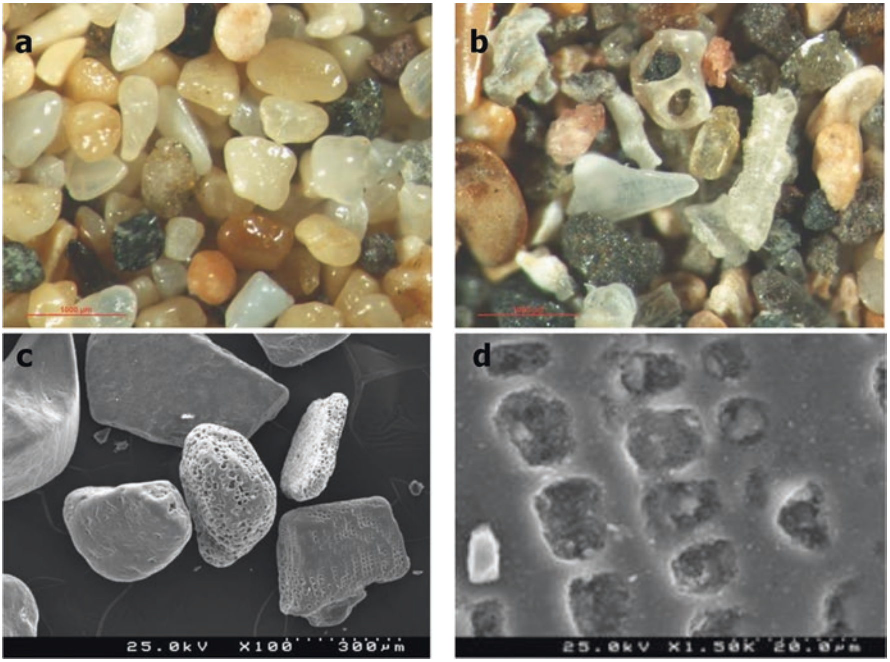


Fig. 12.3 Bioclasts of the biogenic carbonate sand of Porto Santo Island. (**a**) Top left; (**b**) top right; (**c**) bottom left; (**d**) bottom right

Table 12.1 Chemical composition of the major chemical elements (in %) of the biogenic carbonate sand from Porto Santo Island

SiO_2	Al_2O_3	TiO_2	Fe_2O_3	MnO	CaO	MgO	K_2O	Na_2O	P_2O_5	P.R.
6.10	1.90	0.09	0.51	0.03	47.12	2.69	0.06	0.43	0.25	40.14

thermal behavior of the sand when in the natural environment on it there is strong sun exposure that promotes high rise of temperature that can reach 65 °C and the low diffusivity of the heat verified when the sun exposure is momentarily interrupted.

Remains of algae belonging to the Corallinaceae family and to the Corallinoideae subfamily with particularly arborescent forms of the genus *Lithothamnium* are well represented in the carbonated biogenic sand of Porto Santo.

In the chemical composition of the sand, the high Ca, Mg, Sr, Zn, P, and S contents are salient (see Tables 12.1 and 12.2).

Besides the mineralogical and chemical properties, the physical properties, more precisely the thermal properties of sand, are also interesting. Effectively, in the natural environment and particularly in summer, the sand absorbs solar radiation and can reach at the surface the temperature 65 °C, and about 4–5 cm underneath the surface, the sand temperature is not higher than 45 °C. Baths lasting time and sand cover thickness obey to empirical control.

Table 12.2 Chemical composition of the minor and trace chemical elements (in ppm) of the biogenic carbonate sand of Porto Santo Island

Sr	Ba	Zr	As	Zn	Ni	Cu	Cr	S	V
1.321	105	19	1	22	5	4	1	48	5

The sand heated by solar radiation when covering parts of the body in the outdoor baths or heated to reach temperature around 40–42 °C by other means in clinics of geomedicine or in thalassotherapy centers, i.e., temperature in both cases higher than that of the human body, makes it to transpire. The duration of sun-baths is 20–30 min.

During sand-bathing, the human body receives and stores heat, and the acid sweat (pH = 4.1–6.5) being produced reacts with the carbonate sand, liberating in the ionic form, Ca^{2+}, Mg^{2+}, Sr^{2+}, P^{5+}, and the other existing cations, which are freed at skin surface, can be absorbed through it. The eliminated acidic sweat promotes the fixation of the fine and tabular particles of the sand leading to the formation of a coating few millimeters thick, and promotes too the dissolution of the carbonates of the sand, passing to the sweat developed in the body/sand interface the cations Ca^{2+}, Mg^{2+}, Sr^{2+}, Zn^{2+}, P^{5+}, and other elements extracted from sand coexisting with Na^{+} and K^{+} cations and others eliminated by the body).

The concentration gradients formed, as the body dries, favor the cation exchange process, whereby bivalent cations (Ca^{2+}, Mg^{2+}, Sr^{2+}, Zn^{2+}) are preferentially absorbed through the skin (the surface area of the skin in the body of an adult human is estimated at 1.5 m^2), which functions as a semipermeable membrane. In 1 cm^2 of the skin, there are on average 1 m of capillary blood vessels, 4 m of nerve fibers, 3 million cells, 100 sudoriparous glands, 15 sebaceous glands, and 100–500 sensory receptors.

Experience has shown that the therapeutic properties of Porto Santo's biogenic carbonate sand are optimized:

1. As much as the size of sand grains is within the range 0.125–0.250 mm
2. As much as the number of sand grain showing platy shapes increases
3. As much as the number of volcanoclastic and ferromagnetic sand grains increases
4. As much as the number of bioclastic grains of biogenic carbonate sand increases
5. As much as the number of bioclastic grains of calcareous algae increases
6. As much the number of grains of magnesium-calcite (Mg-calcite) increases
7. As much as the contents of Ca, Mg, Sr, P, S, I, and F increases

The mechanism of action of the sand-bath involves both thermal and chemical effects, the first promoting the opening of skin pores what favors the efficacy of the second expressed by the body uptake of the bio-essential elements Ca, Mg, Sr, Zn, Se, P, S, I, and F existing in the sand, which partial dissolution is required. Also, it is essential that the aqueous film formed at the interface body/sand is left to dry during 5–10 min after bathing and before sand removal (seawater-bath or freshwater shower-bath), in order to favor the absorption.

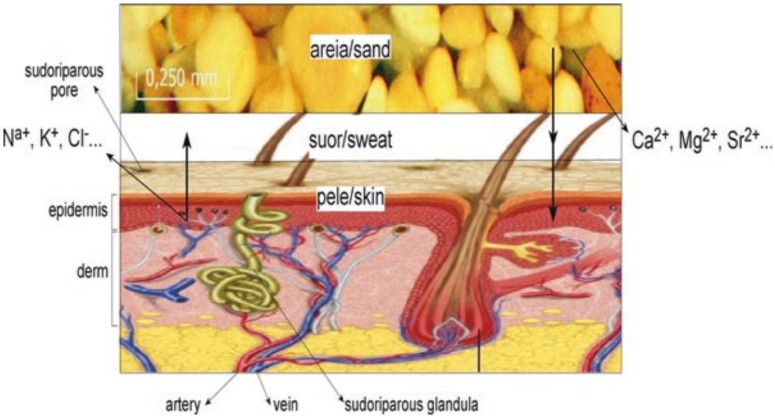


Fig. 12.4 Interaction between the biogenic carbonate sand of Porto Santo and the human body, through an intermediate phase consisting of acid sweat developed at the sand/body interface during the sand-bath whose temperature is higher (40–42 °C) than that of the body human (37 °C); the sweat will provide the partial chemical dissolution of the carbonate sand grains; the Na^+, K^+, and Cl^- ions are released from the body into the sweat, while the Ca^{2+}, Mg^{2+}, and Sr^{2+} essential constituents of the sand are swept into the sweat; at the end of the bath, as the sweat is drying, the Ca^{2+}, Mg^{2+}, and Sr^{2+} ions are absorbed by the body and incorporated into the intercellular and intracellular fluids

Figure 12.4 schematically shows the ion interchange between sand and human skin.

Figure 12.5 shows the dissolution curves for Ca and Mg, corresponding to the interaction of the biogenic carbonate sand from Porto Santo with an acid solution (pH = 5.5) which replicates human sweat.

Whereas Ca/Mg ratio in the bulk sample of Porto Santo is about 20 (see Table 13.1), Ca/Mg ratio shown in the dissolution curves is around 4. This means that Mg related with Mg-calcite enters into solution more rapidly than Ca. Dissolution rates were determined at laboratory temperature (ca. 20 °C), whereas in sand-baths the dissolution of sand by human sweat takes place at twice the temperature of the laboratory. Also, in sand-baths the sweat is being renewed, which explains that the dissolution kinetics would be different from the one verified in the laboratory.

According to Morse and Arvidson (2002), the temperature, the crystalline structure, and the chemistry, as well as the grain size, shape, and porosity of the calcium carbonate species (Mg-calcite, aragonite, and calcite), might influence the dissolution kinetics. The studies CG and JS have carried out using XRD analysis on the dissolution residues of the biogenic carbonate sand from Porto Santo indicate that as the dissolution progresses, the content of Mg-calcite diminishes.

In the last two decades, sand-baths could be practiced indoors, inside local adequate *spa* facilities, as is the case of the Geomedicine Centre & Spa of the Porto Santo Hotel. Currently groups of patients from European Nordic countries are regular users of this spa, the patients being assisted by technical professionals who travel

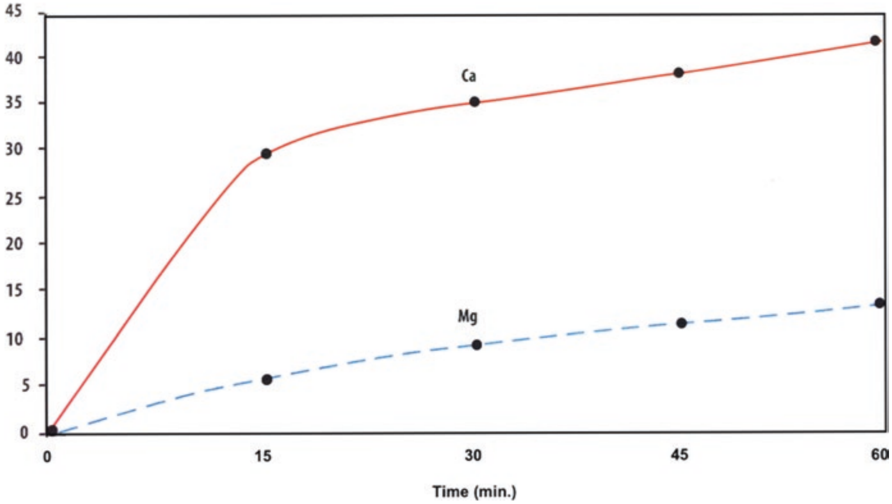


Fig. 12.5 Acid dissolution curves of Ca and Mg determined in a representative sample from Porto Santo biogenic carbonate sand

with those groups of patients. During 1 week, and twice a day, each patient takes a total of 12 sand-baths using the same tube, and when the program is finished, the sand is removed from the tube and exposed to sun radiation for sterilization during 1 week at least.

Every year one group of amputee people from Norway come to Porto Santo for sand-bathing inside the facilities of the Geomedicine Centre & Spa of the Porto Santo Hotel. The Momentum, the Amputee Association of Norway, is the organizer of the psammotherapy treatments, and Nils-Odd TØnnevold, the founder of Momentum and president of the International Confederation of Amputee Associations (IC2A) that gathers the associations of 14 countries, states that the sand-baths significantly diminish the so-called phantom pain.

Figure 12.6 shows some of the steel-made tubes used for sand-bathing in the "Geomedicine Centre & Spa of Porto Santo Hotel.".

Sand is artificially warmed up to 40–41 °C, temperature sufficient to promote the sweating of the human body, sweat that is required to get the partial dissolution of the film of biogenic carbonate sand that is in direct contact with the body, in order to allow the uptake of the bio-essential elements liberated from the sand.

The sand-bath procedure adopted in the "Geomedicine Centre & Spa of Porto Santo Hotel" pretends to simulate the procedure applied in the traditional sand-baths taken in the dry sand of the transition zone beach/frontal dune.

Gomes and Silva (2001, 2007, 2012a, b), Silva (2003), Gomes (2003) and Gomes et al. (2008) have studied and reported the particular features (genetic, textural, mineralogical, chemical, and thermal) of this rare type of sand and determined too

Fig. 12.6 View of one box with two steel-made tubes where sand-baths take place at the "Geomedicine Centre & Spa of Porto Santo Hotel"

the relevant sand properties that could explain the healing effects obtained from sand-baths.

With regard to sand textural features, grain size (almost all sand grains have sizes in the range 0.250–0.125 mm) and grain shape (almost all sand grains are platy and porous) are the most relevant.

In what sand mineralogical composition is concerned, it mainly consists of three carbonate minerals (calcite, Mg-calcite, and Sr-aragonite), all characterized by relatively easy dissolution in acidic solutions, such as the one corresponding to the sweat necessarily formed along sand-bathing procedure on the interface sand layer/human body, provided that sand is warmed up to a temperature higher than the normal temperature of the human body, either in natural environment (solar radiation exposure), or in artificial environment and conditions (inside appropriate spa facilities).

Experience shows that the maximum health benefit of sand-bath comes if once finished the sand-bath, and before removing the sand using a shower, the patient keeps the sand fixed to the skin for few minutes until the skin gets fully dry. This procedure potentiates the uptake of the bio-essential elements liberated from carbonate dissolution.

The effects of musculo-skeletal inflammation, osteoarthrosis and fibromyalgia, are known to benefit from the effects of heat or from the chemical absorption of relevant chemical elements, thus resulting not in the cure of diseases, but rather in the improvement of quality of patients, for a longer or shorter time (10–15 weeks).

The incorporation of the chemical elements provided by the biogenic carbonate sand may also be provided through ingestion using dietary diets based on vegetables and fruits grown on the soils of the south coast platform of the island which are developed on sand of the referred type. The chemical analyses carried out on vegetables and fruits evidenced the relatively high concentrations of Ca, Mg, Sr, Zn, P, and S. Water from local springs, equally rich in the chemical elements mentioned, can also be introduced in the diet.

The quality of the natural resources of Porto Santo Island allows the classification of the island as a singular Natural Health Resort (Gomes and Silva 2012a, b).

12.3 Bathing in the Naturally Warm Volcanic Sands of Southern Japan

For more than 300 years, Japanese have traveled to Ibusuki's shoreline in search of a sandy cure for rheumatism, back pain, post-stroke paralysis, hemorrhoids, asthma, diabetes, menstrual disorder, infertility, anemia, constipation, obesity, and all sorts of other things the warm sand (50–55 °C) is said to cure.

This healing power lured both ordinary Japanese and historical figures like Shimazu Nariakira, a powerful daimyo (feudal lord) who built a manor house on the edge of one of the hot springs near Ibusuki City.

In modern times, *suna-mushi*, i.e., sand-bathing, has also evolved into a beauty treatment, a means to moisturize the skin via metasilicic acid and calcium ions with origin in the sand.

Eager for proving the veracity of these health and beauty claims, Japanese researchers have put the black sands through a battery of scientific tests in recent years. For instance, a study by the medical department at Kagoshima University determined that inhaling the steam that filters through the sand increased cardiac output and improved blood circulation by a factor three to four times greater than the steam generated by average hot springs.

Fifteen to twenty minutes beneath the sand is the recommended bathing time – enough time to inhale a fair amount of geothermal steam and to get the sweat glands to expunge toxins. Dermal absorption of the warm alkaline moisture responsible for sand permanent wetness, rich in Mg, Ca, Fe, and other elements, could be the cause of the produced beneficial effects. Freshwater showers can wash out the sand from the body, after which the bather can sink into the relaxing hot spring pools – the final part of the Ibusuki beach experience.

Only in Ibusuki, at the southernmost tip of the Satsuma Peninsula, is possible to enjoy sand-bathing (Fig. 12.7). Some audacious claims are made about sand-bathing health benefits. Apparently, it is good for lumbago, infertility, diabetes, anemia, and asthma. It also aids weight loss and "total body beauty."

On sunny days, like in Porto Santo Island, a small umbrella is used to shield bather's faces from direct sun radiation. Then, the attendant quickly will cover bathers from the neck down in the volcanic sand. Once all the areas of the sand-bath being utilized, the sand is then sanitized with heated water so that no one is ever being covered in sand that was used to cover someone else.

Fig. 12.7 Sand-bathing in Ibusuki, at the southernmost tip of the Satsuma Peninsula

12.4 Bathing in the Radioactive Monazite-Rich Sands from Guarapari, Brazil

Some of the atoms of the chemical elements making minerals, such as Th, Ac, U, and Ra, are unstable and change quite naturally into atoms of other elements, a process that implies the emission of ionizing radiations. Such process is called *radioactivity*, the unstable atoms are called *radionuclides* or *radioisotopes*, and the changes referred to are called *radioactive decays*. The rate of decay of an unstable radionuclide is expressed by a parameter called half-time, which is the period of time in which half of the original number of atoms will have decayed.

The spontaneous emission of helium or α-particle from the thorium nucleus is called “thoron” or ^{220}Rn, whereas that of radium is called “radon” or ^{222}Rn and that of actinium is called “actinon” or ^{219}Rn.

Areas of high natural radioactivity include places where monazite-rich sands occur as happens in Brazil, China, Egypt, and India; places where uranium mineralization occur as happens in France, the United Kingdom, the United States, and Portugal; and places where certain volcanic rocks occur as happens in Brazil, South Africa, Angola, and Italy.

Guarapari is a coastal town of the state of Vitória do Espírito Santo, Brazil, and a popular tourist destination; its beach is famous for the high natural radioactivity level of its sand. Guarapari is known as the Health Town, due to its beautiful beaches of monazite-rich sands, which manifest natural radioactivity (Fontana 2002).

Monazite (Ce, La, Y, Th) PO_4 is a brown-yellowish mineral of prismatic or tabular crystal habit, chemically a phosphate rich in Ce, La, Y, Th, and other rare earth elements, which occurs as an accessory mineral in certain types of rock, such as gneiss, pegmatite, and carbonatite, and whose alteration, disintegration, and erosion cause the release and concentration of *monazite* on the bed of water courses and on fluvial and marine placers. It is assumed that Guarapari monazite has origin in the metamorphic complex of Serra do Mar, one of the oldest mountainous ranges of the planet. Monazite is a heavy mineral, whose density is estimated at 4.9–5.4 and which occurs associated to other minerals, ilmenite, garnet, and zircon, in the sand of certain beaches of Guarapari (Areia Preta, Meaípe, Setiba, Ipiranga, Riacho, and Morro da Pescaria). The Guarapari monazite-rich sands were discovered in 1898, and after being exported to France, 3–6% of ThO was extracted from them.

The citizens of the town of Guarapari which was founded by a priest, Padre José de Anchieta, in 1585, are not normally afflicted by disease, making this a place of happiness, where the number of nonagenarians is much higher than in Vitória, the capital of the Espírito Santo State, and in the interior of this same state. After José Anchieta, António Silva Melo was one of most important persons in the history of Guarapari, since it was him who discovered and revealed the therapeutic properties of Guarapari beach sand, making Guarapari balneary resorts famous worldwide.

António da Silva Melo (1886–1973) was a Rio de Janeiro physician, who wrote a PhD thesis on the topic "*Estudo do efeito do Tório X sobre o Sangue*" published in the "*Zeitschrift fur Klinische Medizin*," one of the most important scientific journals

Fig. 12.8 Monazite-rich sand existing in the Meaípe Beach, Guarapari, Brazil

of pre-World War I Germany. Silva Melo arrived in Guarapari in 1938 and discovered the radioactivity of its beach sand.

Figure 12.8 shows people sand-bathing in the Meaípe beach, in Guarapari.

In fact, there are three naturally occurring radon (Rn) isotopes, ^{222}Rn being the main radon isotope of concern to man. It occurs in the ^{238}U decay series and has a half-life of 3.82 days, providing about 50% of the total radon dosage to the average person, whereas ^{220}Rn is produced in the ^{232}Th decay series. α-Particles (or helium nucleus), having relatively high mass, are characterized by low penetrating power, whereas β-particles (electrons or positrons), having much lower mass, are characterized by high penetration power in matter.

Silva Melo (1971) described the relevant properties of the monazite-rich sands in his book "*Guarapari, Maravilha da Natureza*," i.e., "*Guarapari Natural Wonder*." Measurements then carried out detected γ-rays up to nearly 1 m above the ground, whereas α-rays were detected at ground level and β-rays a little above the level at which α-rays were detected. Silva Melo recommended the exposure to the radioactivity emitted by the monazite-rich sand for the treatment of health affections, such as muscular and articular rheumatism, arthritis of diverse etiologies, neuralgies, and myalgies.

The effect of ionizing radiation on human health has led to much interest in measuring the background radiation all around the world and in the monazite-rich sands of Guarapari in particular as well as of their medicinal properties and applications (UNSCEAR 2000; Moura et al. 2002; Moura 2003; Vasconcelos et al. 2009, 2011, 2013; De Prá et al. 2015; Lazzerini et al. 2018).

Vasconcelos et al. (2013) investigated the natural radiation source from monazite sand that enhances the exposure of tourist in beaches. The authors have investigated the gamma activity of radioisotopes, such as ^{232}Th, ^{226}Ra, and 40K, in samples of beach sand from Guarapari and estimated the absorbed dose rate, and the effective dose rates were calculated and compared with internationally accepted values as well as other HBRAs.

In certain beaches of Brazil, there are areas well known for their high background radiation; Guarapari is an example, where the local geological controls and geochemical effects cause enhanced levels of terrestrial radiation. Presence of monazite sand explains the high background from Guarapari and other regions along the Atlantic coast from Brazil.

> The observation that there are no noteworthy adverse health effects in some of the world very high-level natural radiation areas brings into question the 'safety levels of radiation'. In some areas in the world, the natural radiation doses to man and to other biota are many hundreds of times higher than the currently accepted dose limit for the general population. No adverse health effects were found in humans, animals and plants in these areas (Jaworowski 2000, *In:* "Introduction to 'Medical Geology: Focus on Tropical Environments'.

References

De Prá W, Lazzerini FT, Orlando MID (2015) Biologically active components (BAC) in Monazite Beach sands – radon climatic Thalasso SPA town, Guarapari/BRA. Congreso Internacional del Aqua – Termalismo y Calidad de Vida. Campus da Auga, Ourense, Spain, 2015

Federicci PC (1980) Sabia, limi e alghe nella Talassoterapia. In: Gualterotti (ed) Proceedings of the I World Thermalism Congress in progress in medical hydrology, Climatotherapy and Thalassotherapy, Lido di lesolo, Venezia

Fontana P (2002) Guarapari. Gráfica Primos Lda

Gomes CSF (2003) How minerals are important for human health. In: Ferreira MRP (ed) A Geologia de Engenharia e os Recursos Geológicos. Imprensa da Universidade, Coimbra, pp 379–390

Gomes CSF, Silva JBP (2001) Beach sand and bentonite of Porto Santo island: potentialities for applications in Geomedicine/Areia de praia e bentonite da ilha do Porto Santo: Potencialidade para Aplicações em Geomedicina. Edição dos autores, 60pp. ISBN: 972-8684-05-03

Gomes CSF, Silva JBP (2007) Minerals and clay minerals in medical geology. Appl Clay Sci 36:4–21, Elsevier

Gomes CSF, Silva JBP (2012a) Ilha do Porto Santo: Estância balnear de saúde Natural/Porto Santo Island: Unique Natural Health Resort. Madeira Rochas-Divulgações Científicas e Culturais (ed), Funchal, RAM, 237pp

Gomes CSF, Silva JBP (2012b) Psammotherapy in Porto Santo island, Madeira archipelago. Anales de Hidrologia Médica, vol 6, Universidad Complutense de Madrid

Gomes CSF, Silva JBP, Sequeira ME, Gomes JH (2008) Potentialities for therapeutic purposes of the biogenic carbonate sands occurring in some islands of the Macaronesia' archipelago based on their unique chemical and physical properties. Geochim Bras 22(3):332–343

Jaworowski Z (2000) Ionizing radiation and radioactivity in the 20th century. International conference on radiation and its role in diagnosis and treatment. FICR-2000 Tehran, Iran Oct 18–20

Lazzerini FT, Orlando MT, De Prá W (2018) Progress of negative air ions in health tourism environments applications. Bol Soc Esp Hidrol Méd 33(1):27–46. https://doi.org/10.23853/bsehm.2018.0450

Melo AS (1971) Guarapari, Maravilha da Natureza. Editora Cruzeiro, 230pp

Morse JW, Arvidson RS (2002) The dissolution kinetics of major sedimentary carbonate minerals. Earth-Sci Rev 58:51–84

Moura JC (2003) Estudo da variação sazonal dos níveis de radiação gama na praia da Areia Preta, Guarapari, Espírito Santo, Brasil: Radiometria e Analise de Risco Ambiental. Dissertação de Mestrado em Engenharia Ambiental do Curso Tecnológico da Universidade Federal do Espírito Santo (PPGEAICT/UFES), Vitoria

Moura JC, Wallfass J, Bossew CM (2002) Health hazards of radioactive sands along the coast of Espirito Santo, Brazil. Neues Jahrbuch fur Geologie und Palaontologie, vol. 225, no. 1, pp 127–136. Stuttgart, Alemanha

Murgia A (1980) Hipótesis sul le mecanismo d'aczione della psamoterapia. In: Gualterotti (ed) Proceedings of the I World Thermalism Congress in progress in medical hydrology, climatotherapy and thalassotherapy, Lido di Lesolo, Venezia

Silva JBP (2003) Areia de praia da ilha do Porto Santo: Geologia, génese, dinâmica e propriedades justificativas do seu interesse medicinal. Madeira Rochas-Divulgações Científicas e Culturais (editor), 345pp. ISBN: 972-99004-0-X

UNSCEAR (2000) United Nations Scientific Committee on the effects of atomic radiation (2000): sources and effects of ionizing radiation. Report to general assembly, with scientific annexes, United Nations, New York

Vasconcelos DC, Oliveira AH, Silva MRS, Penna R, Santos TO, Pereira C, Rocha Z, (2009) Natural radioactivity in extreme south of Bahia, Brazil using gamma-ray spectrometry. International nuclear Atlantic conference, Rio de Janeiro, September 27 to October 2

Vasconcelos DC, Pereira C, Oliveira AH, Santos TO, Reis PL, Rocha Z (2011) Natural radioactivity in sand beaches of Guarapari, Espírito Santo state, Brazil – a comparative study. International nuclear Atlantic conference – INAC 2011, Belo Horizonte, MG, Brazil, October 24–28, Associação Brasileira de Energia Nuclear – ABEN ISBN 978-85-99141-04-5

Vasconcelos DC, Reis PA, Pereira C, Oliveira AH (2013) Modelling natural radioactivity in sand beaches of Guarapari, Espirito Santo State, Brazil. World journal of nuclear science and technology 3(02), 65–71, https://doi.org/10.4236/wjnst.2013.32011

Chapter 13
Mineral Water: Essential to Life, Health, and Wellness

Frederico J. Teixeira and Celso S. F. Gomes

Abstract Mineral water is the natural water that is essential to life, health, and wellness and comes from aquifers, either superficial or underground, through pumping, deep wells, and springs. Mineral water is an essential constituent of the human body. Mineral water is rich in minerals and is used as it is or after undergoing purification. In general, mineral water for human consumption undergoes physical and chemical treatments, microbiological control, and monitoring too to ensure maximum purity. It is known for centuries that minerals existing in solution into drinking water are essential for humans, animals, and plants, different minerals having different functions. Water is an essential constituent of the human body, and minerals condition the physical, chemical, and physicochemical properties of the drinking mineral water that should be safe not only chemically but microbiologically too. Water quality issues are a major challenge that humanity is facing in the twenty-first century. The chapter reports basic and actual information on mineral water as an essential constituent of the human body and health conditioner, as well as on sources and resources, on sanitary safety, and on typologies and functions.

13.1 Background Data on Mineral Water

Water quality issues are a major challenge that humanity is facing in the twenty-first century. Schwarzenbach et al. (2010) have reviewed the main groups of aquatic contaminants, their effects on human health, and approaches to mitigate pollution of freshwater resources. Emphasis is placed on chemical pollution, particularly on inorganic and organic micropollutants including toxic metals and metalloids, as

---

F. J. Teixeira
Faculty of Medicine, University of Coimbra, Coimbra, Portugal
e-mail: fredjt@uc.pt

C. S. F. Gomes (✉)
Department of Geosciences, Researcher of the Research Unit “GeoBioTec”,
University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_13

well as a large variety of synthetic organic chemicals. Geogenic contamination of underground waters and mining operations' contamination of surface waters are important sources of inorganic pollutants.

The so-called waterborne diseases are due to chemical contaminants and to pathogens present in drinking water. Climate changes, increasing water temperature, severe rainfall, and flooding events will favor the spread of waterborne diseases, in particular infectious disease outbreaks, such as yellow fever, malaria, and dengue (Myers and Patz 2009; WHO 2007).

Mineral waters can be classified according to their origin:

1. Meteorological – those existing in superficial aquifers produced by rain, snow, and de-icing
2. Juvenile – those that see daylight when surfacing
3. Fossil – those existing in confined underground aquifers, either in continental areas or in sea areas

There are different categories of waters intended for human consumption, such as *natural mineral waters* and *spring waters*:

1. Natural mineral waters may be distinguished from ordinary drinking mineral water by their *purity* at source and their *constant level of minerals*; spring waters are intended for human consumption in their natural state and are bottled at the source.
2. Directive 2009/54/EC regulates the marketing and exploitation of natural mineral waters. Certain provisions of this Directive are also applicable to spring waters such as the microbiological requirements and labelling requirements.
3. Commission Directive 2003/40/EC of 16 May 2003 establishes the list, concentration limits, and labelling requirements for the natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters.
4. Natural mineral water exploration and exploitation is conditioned to an authorization procedure carried out by the Competent Authorities of the EU Member States.

13.2 Mineral Water: Sources and Resources

On the one hand, the current "best guess" for liquid water appearance on Earth, in the so-called primitive oceans, was around 4.4 Ga years ago, the solar system being formed at around 4.6 Ga years ago and the Earth being formed at around 4.5 Ga years ago. Such water would have resulted from both impacts on Earth of *icy* planetesimals similar in composition to comets and the asteroids in the outer edges of the asteroid belt and from the vast cloud of dust and gas remaining after the Sun's formation, called the *solar nebula* (Wu et al. 2018).

Also, Moon-forming impact at around 4.5 Ga ago between the two young planets Earth and Theia would have vaporized much of Earth's crust and upper mantle and created a rock vapor atmosphere around the Earth which is unique among the rocky planets in the solar system in that it is the only planet known to have oceans of liquid water on its surface.

In the case of Earth's oceans, the deuterium-to-hydrogen or ^{2}H-to-^{1}H ratio is close to what is found in asteroids, the reason why scientists have long thought that most earthly water came from an asteroid bombardment in the days of the early solar system.

On the other hand, the current "best guess" for the earliest appearance of life on Earth is around 4–3.8 Ga in the transition of the Hadean geological eon (~4.5 Ga–4.0 Ga) to the Archean geological eon, and the first life forms of single-celled organisms most probably based on RNA may have been developed in undersea alkaline vents, this being a hypothesis like others referred to in Chap. 7 of this book.

In the late Hadean, the Earth's atmosphere consisted largely of water vapor, nitrogen, and carbon dioxide, with smaller amounts of carbon monoxide, hydrogen, and sulfur compounds (Kasting 1993; Genda 2019).

The appearance of oxygen in the atmosphere probably at around 2.3 Ga years ago is mainly the result of photosynthesis in cyanobacteria – the only bacteria that produce oxygen as a byproduct of their metabolism, using light, water, and carbon dioxide to produce oxygen and biomass. It was not until these creatures appeared on Earth that oxygen was found in the Earth's atmosphere, which played a key role in the evolution of single-celled organisms to multicelled organisms. To build up one complex multicellular organism, energy is needed, and the oxygen would be the trigger to get such energy.

About 71% of the Earth's surface is covered by water with a total estimate of 1.4×10^{9} km^{3}. The Earth's surface oceans appear to have existed since very early in the Earth's history, perhaps even since the Earth's formation, and the presence of oceans distinguishes Earth from other planets in the solar system. However, the mass of the Earth's oceans (Moce = 1.4×10^{21} kg) is only 0.023 wt% of the planet's total mass (ME = 6.0×10^{24} kg). Even if the water in the Earth's interior (the mantle and core) is taken into account, the mass fraction of water does not exceed 2 wt% of the total planetary mass (Genda 2016). The water content in the Earth's mantle can be estimated to be from one to ten times the present ocean mass.

The suitable distance of Earth from the Sun (the central star of the solar system) is the most important factor determining the stability of liquid water on the Earth's surface, shorter distance would cause water vaporization, and longer distance would cause water congelation. The adequate distance of Earth from the Sun and a suitable amount of greenhouse gases in the Earth's atmosphere have made this planet habitable. H_2O molecules are expected to be abundant in the solar system because hydrogen is the most abundant chemical element in the solar system.

From outer space, the Earth looks like a "blue planet" because most of its surface is covered by water, particularly in the oceans.

Only 2.5% of that water is fresh, and most of that lies frozen and inaccessible in the icecaps and Greenland, leaving less than 1% of fresh water accessible in lakes, river channels, and underground. A significant amount of water is also stored in the Earth's crust, mantle, and core existing primarily in hydrated minerals, most phyllosilicates exemplified by clay minerals. Also, only about one-third of the world's potential fresh water can be used for human needs. As pollution increases, the amount of usable water decreases. Water pollution is due to two main pollutants: chemical (geogenic inorganic both natural and derived from mining practices mainly from tailings and synthetic organic) and pathogenic. Geogenic inorganic pollutants include heavy metals (e.g., Cr, Ni, Cu, Zn, Cd, Pb, Hg, and U) and metalloids (e.g., Se and As). Synthetic organic pollutants include pesticides, biocides, and pharmaceuticals.

Water contributes significantly to health, and good health is the essence of development. However, water's protective role is largely unseen and taken for granted in the wealthier countries. Its contribution to health is directly within households through food and nutrition and indirectly as a means of maintaining a healthy, diverse environment. These two precious resources – water and health – together could enhance prospects for development.

In humans, about 60–65% of the body weight is represented by total body water (TBW), distributed into intracellular and extracellular fluid compartments, which contain about 65% and 35% of total body water, respectively. In the body of a young adult weighing 60–70Kg, there are 40–42 liters of water. In general, men have more 15% of water than women. The water referred to is not pure water; it contains diverse chemical elements in the ionic form (e.g., Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^-, CO_3H^-, PO_4^{3-}) all essential to life, whose nature and concentration depends upon the cellular function.

The cell membrane regulates the ion exchange between the aforesaid compartments, but water concentration is always maintained. In the extracellular liquid predominates Na^+, Cl^-, and CO_3H^-, whereas in the intracellular liquid predominates K^{1+}, PO_4^{3-}, organic acids, and proteins. Perfect health requires the "dynamic equilibrium" or "hydroelectrolitic equilibrium" between the contents of both intracellular and extracellular compartments. Any rupture of such equilibrium could result from excessive ingestion of food (water included) or excessive water loss and naturally of the minerals in the ionic form it contains due to excessive sweating related to work and heat exposure or to disease (diarrhea or vomits) which could cause dehydration and eventual death.

Water is involved in many bodily functions, since it serves as a carrier of nutrients and substances in the circulatory system. Furthermore, it is the vehicle to excrete products and eliminate waste and toxins, and it also lubricates and provides structural supports to tissues and joints. However, there is no efficient mechanism of body's water storage; therefore, a constant supply of fluids is needed to keep water content.

Natural water can be sweet or fresh and salty. Of all the water that exists in the planet, about 97.5% is salty, that is, it is in the oceans and seas, and its volume is estimated at 1300 million km^3. And, 2% of the water present on Earth is in the form of glacial ice on the north and south poles of the Earth.

It should be noted that the water molecule is the most amazing and abundant molecule in the universe. The water molecule consists of the association of two hydrogen atoms (H) attached to one oxygen atom (O) making the bonds with an angle of 104°. Thus, the water molecule is morphologically symmetric but electrically asymmetric and dipolar: on one side it has a negative electric charge; on the other side it has a positive electric charge. The relatively strong hydrogen bonding between water molecules gives water its relatively high melting and boiling temperatures.

In more detail the water molecule (H_2O) is a complex body resulting from the combination of three isotopes of oxygen (^{16}O, ^{17}O, ^{18}O) and three isotopes of hydrogen (^1H, ^2H called *deuterium*, and ^3H called *tritium*). With regard to oxygen isotopes, the relative abundance is as follows: ^{16}O (99.762%), ^{17}O (0.038%), and ^{18}O (0.200%). With regard to hydrogen's stable isotopes, the relative abundance is as follows: ^1H (99.985%) and ^2H (0.015%). Isotopes of one chemical element are just distinguished by the number of neutrons existing in the element nucleus.

The so-called isotopic hydrology or isotopic hydrochemistry is of paramount importance to determine the source of the water reservoirs or aquifers, the recharge processes, and the characterization and understanding of the relationships between underground aquifers and surface aquifers.

The stable isotopes ^{18}O and ^2H are intrinsic tracers of the water molecule and of the total water cycle that is a characteristic of our planet. These and other achievements are the result of the recent developments on isotopic analysis, as is the case of mass spectrometry with plasma source and multi-collection MC-ICP-MS (multi-collector inductively coupled plasma mass spectrometry).

A hydrogen atom (H), the smallest and simplest chemical element, has only one electron which is easily shared by an oxygen atom (O), which is electronegative and seeks to attract electrons. In the presence of hydrogen atoms, each oxygen atom attracts two hydrogen atoms. In the water molecule, the chemical bonds between O and H are covalent, and when several water molecules are present, hydrogen bonds or bridges are formed between the molecules responsible for the expansion when solidification or freezing occurs. Water molecules characterized by constant vibration and interaction bond tightly to one another. When the water freezes, an ordered structure of hexagonal crystals is formed, supported by regular hydrogen bonds.

Given both oxygen and hydrogen in the form of gases in the Earth's atmosphere, it could be assumed to be easy to make water by forced collision between them. But this is not so because the reaction involved is generating a large amount of energy and may even be explosive. Therefore, the alternative to the production of water in this way is the extraction of water already present in the atmosphere in the form of steam through a process called condensation. For this purpose, when using chilled metal blades, the temperature of the surrounding air decreases rapidly, the water vapor condenses, and the water production takes place. The *Whisson windmill* is the material expression of this process. When cooled the blades spin; they can condense up to 12,000 l of water every 24 h. The chemical elements oxygen (O) and hydrogen

(H) are, among all the natural chemical elements, the largest formers of minerals. Water is a constituent of many minerals, particularly silicates that dominate the Earth's crust, and can participate in two chemical forms: H_2O and HO (hydroxyl).

On Earth, water is the only natural substance that can occur in three distinct physical states: liquid, solid, and gas. Switching from one state to another does not involve chemical changes requiring only an increase or decrease in energy, in the form of heat or pressure.

In liquid water the molecules move freely occupying a defined volume, but if cooled the molecules lose kinetic energy and approach a rigid structure called ice (freezing). However, if the liquid water is heated, that is, by adding energy, the movement of the molecules accelerates progressively increasing the free energy until it passes to the state of water vapor or gas (evaporation). This water vapor, if it is cooled, releases energy, which allows the movement of water molecules to slow down until liquid water (condensation) forms.

Water is also present in other asteroids. For example, in the Moon it occurs as ice water at the poles, and on Mars there is information that liquid water has existed in the past. Even comets are true cold-water warehouses, and in the first million years of the Earth, this would have suffered numerous comet impacts, assuming that 30% of the water on Earth has originated in comets.

The Moon, Earth's natural satellite, would have been the result of a massive collision that shortly after the Earth's formation about 4.5 Ga ago would have occurred between a huge unknown star and Earth, a collision that would have provided a start part of the Earth.

A team of specialists in planetary geology at Brown University, in Providence, and the Carnegie Institution, both in the United States, has recently admitted that the portion ripped from the Earth and made into the Moon took with it some of the water that would already exist in the so-called proto-Earth, justifying the fact that the Moon has water inside under the mantle and also at the surface in the form of ice. The team of researchers came to this conclusion after analyzing samples of lunar rocks brought to Earth by the Apollo XV and Apollo XVI missions, and the analyses confirmed the presence of hydrogen and deuterium (the heavier isotope of hydrogen). The obtained measurements are consistent with the measurements obtained in meteorites of the chondrocyte type, whose water has the same geochemical signature of the water present on Earth. The water then in the proto-Earth would have been transferred to the Moon after surviving the vaporization produced by the gigantic impact referred to above. If so, the impacts of chondrite type meteorites (stony meteorite containing small round and glassy granules called chondrules) as well as the aforementioned impacts of comets will be a common source of Earth and Moon water.

It is interesting to note that there are researchers who admit the existence of an immense reservoir of water in the deep interior of the Earth, in the zone of transition of the upper mantle to the lower mantle, between 410 and 660 km of depth. This hypothesis was very recently supported on investigation whose results are reported in the scientific journal *Nature* dated of March 2014, regarding the discovery in Brazil of *ringwoodite*, mineral (previously only identified in meteorites rather than Earth) included in a diamond that had been harvested in 2009 in the region of Juína, Mato Grosso.

The mineral *ringwoodite*, a high-pressure polymorph of the mineral named *olivine*, $(Mg,Fe)_2SiO_4$, and containing 1.5% water, would have been brought from the abovementioned depths to the surface associated with a kimberlite by volcanism. If this large reservoir of water present in the interior of the Earth is confirmed, it could have an important influence on marked geological phenomena such as plate tectonics and volcanism and justify a revision of the theories that explain these natural phenomena.

Less than 1% of the water present on Earth is liquid fresh water, potentially available for drinking, irrigation, and industrial use. And, much of this water occurs in aquifers, that is, natural, underground reservoirs.

Water is not only the basis for human existence. Also, it could become a fuel for human mobility. In the European Union, automobiles are responsible for about 30% of CO_2 emission. Motor cars 100% electric, and hybrid solutions, are being worldwide sought, and water can provide an important contribution for the electrification solution. Hydrogen could be the nontoxic, insipid, colorless, and odorless *gas fuel* obtained from water electrolysis. The separation of hydrogen from oxygen in water molecules by electrolysis was demonstrated in 1800 by the British scientists William Nicholson and Anthony Carlisle who have used electrical discharges for that purpose. The first automobile using hydrogen as fuel was built by Toyota in 2014, first commercialized in Japan, the USA, Germany, Denmark, and United Kingdom. New generations of cars using *fuel cell* already are more advanced than the electric cars in terms of autonomy, and in the near future the *hydrogen fuel cell* will see increased its capacity.

The so-called *green* H_2 can be obtained through water electrolysis with separation of H_2 molecules from O_2 molecules using electricity from renewable sources, for example, solar energy. The required water can be fresh, desalted water, or treated wastewater. The production of 1 Kg of *green* H_2 requires approximately 9 l of water and 1 Kg of *green* H_2 having an energy power of 40 KWh. *Green* H_2 can be incorporated up to 15% in natural gas and can also replace the so-called *blue* H_2 obtained from the use of natural gas to perform the water electrolysis. Currently, in terms of mobility of light vehicles, the competitiveness of *green* H_2 in relation to the electrical battery, e.g., the lithium battery, is economically debatable. However, for heavy vehicle mobility, the H_2 will be unsurpassed. *Green* H_2 will be soon used as a clean alternative technology in all transportation vehicles which today use fossil fuels, as well as in all industries actually using fossil fuels where production could not be electrified. There are great expectations about the decisive contribution of *green* H_2 for significant world decarbonation.

In Portugal, in 2030, all the required energy is expected to come from renewal sources – water, wind, and Sun. Also, there is a plan to initiate in 2022 the production of *green* H_2, the source being seawater in the industrial pole of Sines located in the southwest coast of the country. Sines is the main port in the Ibero-Atlantic front being an open deepwater sea port with excellent maritime access and offering unique natural characteristics to receive any type of vessels, where exists a worldwide extent logistic platform able to receive the main players of port, maritime, industrial, and logistic sectors. Unlike the fresh mineral water from surface and underground reservoirs, ocean water is inexhaustible. Expectations are high regarding the decisive contribution of *green* H_2 for the total decarbonation of the Portuguese energy sector. The energy required to perform the water electrolysis would come from solar energy.

The water used by humanity, which depends on it, has three main sources: surface water (rivers and lakes), groundwater, and atmospheric water (rain). About 70% of the water extracted from the environment, both superficial and underground, is used in agriculture, 23% is used in industry, and 7% is used in our homes.

In the natural environment, there is another type of water that is salty, which is called salt water that occurs in the seas and oceans, making up about 97% of the total water of our planet. In many coastal areas, the fresh drinking underground water is progressively getting salty, a situation that inhibits its drinking and crop growth in agriculture. Such is due to marine salt intrusion into groundwater aquifer owing to overexploitation of aquifers and to sea level rise.

The salts existing in the water of seas and oceans come from the dissolution of minerals from rocks, sediments, and soils that exist in the surface layers of the continents, from rocks and sediments that exist at the bottom of the seas and oceans, and from submarine volcanic emissions and atmospheric deposition.

Salt water in relation to fresh water has a lower freezing point, i.e., it freezes at the lowest temperature, has a higher density, has a higher electrical conductivity, and is slightly alkaline or basic (pH between 7.5 and 8.5), and as opposed to which, it is, as a rule, slightly acidic (pH between 5.5 and 6.5).

Almost all water is in the seas and oceans and is not used for human consumption. But the water of seas and oceans is home to three-fourths of all life on Earth. Only about 3% of fresh water exists on Earth but three-fourths of it is permanently icy. Therefore, only 1% of the Earth's water is available for human use, and to be drinkable it must be colorless, odorless, and tasteless.

Pure fresh water has pH = 7, but as a rule, the fresh water that is ingested has a pH lower than 7, and in a smaller number of cases, it may have a pH higher than 7. Human blood has pH within the range 7.35–7.45, a value strictly regulated by organs like lungs and kidneys. The pH scale ranges from 0 (the most acidic term) to 14 (the most basic term). Rainwater, as a rule, has pH between 4.2 and 4.4. Vinegar and lemon juice have pH values close to 2.

Already it is important to mention that the planet Earth is also known by the name blue planet, because of the blue tonality that it exhibits when it is seen from the space. This tonality is not due to water but rather to atmospheric gases, oxygen, nitrogen, and others. On the surface the seawater displays in many places turquoise color, that is the result of the mirror effect that reflected the equally blue color of the sky when clear.

On average, seawater in the world's oceans has salinity estimated at about 3.5% or 35 g/L (grams per liter). But salinity in the confined water masses (e.g., the Dead Sea that really is a salted lake) can be considerably higher, allowing the bodies to float without the need for normal movement in the normal sea. The anions chloride, carbonate, and sulfate and the cations calcium, sodium, magnesium, and potassium are predominant in the water of oceans and seas. The Dead Sea is a Thalassotherapy Natural Resort of excellence, worldwide.

The oceans and seas are genuine mineral factories or breeding sites, with a strong emphasis on the minerals of the carbonate group, among which the mineral *calcite*, $CaCO_3$, is the most dominant. These carbonates by chemical precipitation or by the accumulation of exoskeletons of various marine beings in the bottom of oceans and seas give rise to the so-called carbonated rocks, among them limestone. Another group of minerals also created by the sea deserves prominence. This is the case of chlorides, represented by minerals *halite*, NaCl, and *sylvite*, KCl.

Oceans and seas play a key role in climate and weather conditions on the continents because they dominate the water and carbon cycles, moderating temperature fluctuations and maintaining the stability of the composition of the atmosphere. In fact, the ocean absorbs, stores, and transports heat. The ocean absorbs about half of the carbon dioxide (CO_2) emitted into the atmosphere. The huge masses of ocean water absorb much of the solar radiation that hits the Earth and release heat through evaporation. In the atmosphere the condensation of the water vapor causes clouds and precipitation or rain.

The ocean and man are closely intertwined. The ocean is a source of food, of oxygen, and indirectly of fresh water, since most of the rain is generated in the ocean. The ocean is a habitat of very diverse ecosystems, some that are independent of solar energy and photosynthesis, but whose distribution is not uniform, more abundant in certain places and scarce in others. The ocean also serves as a way to communicate between people and freight. In addition to the positive effects mentioned above, the oceans can also have negative effects, particularly on human life and property, as hurricanes, typhoons, and cyclones whose devastating effects are well known have their origins in the oceans.

In Portugal, only 20% of the available water resources are used, with the agriculture sector consuming 75%, the energy sector 15%, the urban sector 6%, and the industrial sector 4% of the volume of water available, which necessarily means that the efficiency of water use needs to be improved. In fact, a decade ago the waste of water in agriculture was around 40%. But since then water management has become more efficient. At present, water waste has already fallen to less than 37%, and the National Plan for Efficient Water aims to achieve a goal of 35% in 2020. And, the use of new irrigation technologies and better training of farmers contribute to this.

About 4000 km^3 of mineral water is extracted from surface and underground reservoirs around the world to meet the needs of humanity. In relative terms most of the water used in human activities returns to the environment, only a small part being consumed. It is estimated that about 50% of the water extracted for agriculture is not recovered and is consumed. By contrast, most water used for industrial and household purposes is not consumed. For example, almost all the water used in hydroelectric power plants returns to rivers after use without appreciable change in their properties.

In Portugal, *natural mineral waters* are geological resources that belong to the public domain, that is, their exploitation requires a concession issued by the central government. In turn, spring waters are geological resources that belong to the private domain.

As a final note regarding climate change impacts on ecosystems, particularly on water resources and water quality, the temperature of surface water is expected to increase as a result of global warming. Some human-induced climate change can be mitigated but is considered unavoidable. However, water supply and water quality has received insufficient attention by hydrology experts about the potential impacts of climate changes in air temperature and rainfall, the more frequent droughts in the summer as well as flash-flooding (Delpla et al. 2009; Whitehead et al. 2009). Climate change impacts on surface water systems are easier to investigate on regional and local scales than on a global scale. Consequences on chemical and microbiological water quality are expected. In Western Europe metal concentrations in rivers and lakes have decreased in the past decades with industrial and urban wastewater treatment efforts. Droughts may have negative impacts on metal concentration, and any decrease in inorganic and organic colloids responsible for metal complexation and deposition will cause metal and microbial increase in the water. There is an urgent need for water quality monitoring.

The global surface temperature has increased by 0.74 °C during the past 100 years (1906–2005) according to the International Panel on Climate Change (IPCC) following the Bali Conference (Rosenzweig et al. 2007). Global warming is an indisputable fact, and the average rate of warming over the last 50 years (0.13 ± 0.03 °C per decade) is nearly twofold higher than that observed over the last 100 years (Trenberth et al. 2007).

The impact of climate change on water resources physicochemical parameters, micropollutants, and biological parameters has been a matter of concern, on both global and regional and local scales, among scientists and the governments of all countries (Xia et al. 2014). At last, concerns are growing over surface water quality due to widespread microbial contamination of water systems (Islam et al. 2018). Increasing temperature and change in rainfall patterns combined with socioeconomic factors, such as human and animal population growth and land use changes, will continue to affect flows and water quality in river systems globally (Jin et al. 2015).

13.3 Drinking Mineral Water: Typology and Function

13.3.1 Basic Information

The fresh mineral water consumed by man is classified into three fundamental types: *natural mineral water*, *spring water*, and *tap water*. The first two types of mineral water are underground water and are extracted for consumption from deep or shallow reservoirs, unlike the surface water flowing in rivers and streams and the equally sweet or fresh water that exists in lakes, currently used as tap water at our homes.

Natural mineral water is a water of deep or extensive circulation within the terrestrial crust, bacteriologically acceptable, which presents physicochemical properties stable in its emergence. The reference values for the physicochemical parameters of natural mineral water are defined by Directive 2009/54/EC of the European Parliament and of the European Council of June 18.

The physicochemical parameters of spring water, because its underground circulation is less deep and extensive, are a bit more tolerant, and those parameters are yet more tolerant for tap water. In Portugal, the reference values of the physicochemical parameters of spring water are defined in the Decree Law n.º 306/2007 of August 7.

The water circulating through and across the rocks extracts from them by dissolving the constituent chemical elements of minerals in the ionic form, such as sodium, potassium, calcium, magnesium, iron, silicon, aluminum, etc., and the foregoing water properties may provide therapeutic benefits or simply favorable effects. The emergence of this type of water can be natural (*spring water*) or be captured by means of a borehole more or less deep; in the latter case, the designation of *natural mineral water* does not make total sense.

The nature of the predominant anions and cations in *natural mineral water* determines their chemical composition and nomenclature: sulfate, sulfurous, bicarbonate, chlorinate, silicate, brominate, iodinate, and fluorinate, regarding the predominant anion; and sodium, calcium, and magnesium regarding the predominant cation. Mineral quality and quantity are responsible for mineral water particular profiles, including clearness, color, odor, and taste of both natural mineral water and spring water.

In limestone regions, for instance in the central and southern maritime coasts of Portugal, there is natural mineral water and spring water classified as bicarbonate and calcium-magnesium-bearing hard water. It is water that is easily recognized by the fact that soap does not make or foam when used for washing hands, also because pots, pans and stainless steel from dishwashers are stained after use in kitchens and also because of the dishes and glasses after washing in the dishwashers if they show spleen. To counteract the latter effect referred to, and provide brightness to the washed pieces, it is usual to add purified salt (NaCl) at the start of the wash.

There are *hard* and *soft* mineral waters, the hard ones being characterized by high Ca and Mg contents, despite having other dissolved chemical elements/minerals. *Water hardness* parameter has been relatively undervalued from the health point of view, in particular in medical hydrology.

The concept of total dissolved solids (TDS) in drinking water, as is the case of tap water, is different to the concept of total mineralization (TM); the first, TDS, comprises the inorganic solid constituents also called salts plus small amounts of organic and colloidal matter, particularly polar organic compounds which are dissolved in water, and as so they could not be filtrated; the last, TM, exclusively comprises dissolved minerals in the elemental form, as cations and anions.

Whenever drinking water bears extremely finely particulate suspended solids, these should be filtrated before TDS analytical assessment. Suspended solids will not pass through a filter, whereas dissolved solids will. TDS can be determined by evaporating a prefiltered sample to dryness and then finding the mass per liter of the dry residue of the water sample. TDS is sometimes used as a “watchdog” environmental test. Any change in the ionic composition between testing sites in a stream can quickly be detected using a conductivity probe. Further tests can then help to determine the specific ion or ions that contributed to changes in the initial TDS reading. However, in natural mineral waters due to their deep source and circulation, the organic component content is almost nonexistent, the reason why TDS and TM values corresponding to a certain natural mineral water are coincident or almost coincident. Total mineralization of natural mineral water can change along the hydrological year, and the control of the resulting periodic changes can be done measuring the *specific electric conductivity* (μS/cm), an important water parameter when natural mineral water is used in health resort medicine.

The parameter dry residue (DR) is also used in drinking water characterization, and it is assessed by evaporation of 1 L of water at 180 °C.

TDS, TM, and DR values in waters bearing or originating volatiles when heated up, for instance in the case of bicarbonate waters, are always lower than they theoretically should be, because in the case of bicarbonate waters, bicarbonate HCO_3 decomposes into H_2CO_3 and CO_2, and this being a gas gets evolved.

In the USA bottled water must contain at least 250mg TDS to be labeled as mineral water.

HCO_3 in water is formed by the reaction of CO_2 dissolved in water with Ca- and Mg- bearing carbonate minerals present in soils and rocks. HCO_3 inside the human body is formed from the reaction of CO_2 produced from carbohydrate metabolism with OH from water: $CO_2 + OH \longleftrightarrow HCO_3$, and this HCO_3 being absorbed by the body fluids contributes for their pH increase.

Regarding drinking water mineralization, the European Union legislation proposes the following classification: *very low mineralized* or *hyposaline*, up to 50mgL^{-1}; *low mineralized*, 50–500 mgL^{-1}; *mineralized*, 500–1500 mgL^{-1}; and *highly mineralized* or *hypersaline*, >1500 mgL^{-1}. This classification is currently extended to natural mineral waters used in health thermal resorts where health resort medicine is practiced.

The classification of Krieger (1963) is currently used to classify drinking water into five groups based on TDS: fresh or very low mineralized waters (TDS 0–1000 ppm), slightly saline waters (TDS 1000–3000 ppm), moderately saline waters (TDS 3000–9000 ppm), highly saline waters (TDS 10,000–35,000 ppm), and brine waters (TDS >35,000 ppm).

Based on dry residue (DR) values, mineral waters are classified as follows: fresh water, <2000 mgL^{-1}; brackish water, 2000–5000 mgL^{-1}; salt water, 5000–40,000 mgL^{-1}; and brine water, >40,000 mgL^{-1} (Custódio and LLamas 1996).

In mainland Portugal the fact that about 2/3 of the territory is occupied by granite rocks and similar rocks justifies the figure of about 80% of hypomineralized natural mineral water and spring water.

The estimation of total dissolved solids (TDS) or total dissolved minerals in water could be easily and cheaply assessed measuring the water electric conductivity expressed in millisiemens per meter (mS/m) or millisiemens per centimeter (mS/cm).

Distilled water conductivity is <1µS/cm, rainwater conductivity in clean areas is <1–5µS/cm, hyposaline mineral water conductivity is 30–100µS/cm, hypersaline mineral water conductivity is 250–600µS/cm, and seawater (salinity 3–3.5%) conductivity is 40,000–50,000µS/cm.

13.3.2 Physical, Chemical, Physicochemical, and Microbiological Properties of Water for Human Consumption

It is not only *natural mineral water* that is good for human health. Other groundwater and even surface water are equally good for health and indispensable for human consumption. In the twenty-first century, humanity is facing many problems related to water quantity and/or water quality (UNESCO 2009). And these problems will be aggravated in the future due to climate changes resulting in higher water temperatures, melting of glaciers, more floods and droughts (Huntington 2006; Oki and Kanae 2006).

Regarding human health the most direct impact is the lack of adequate sanitation of safe drinking water. Additional threats include the exposure to pathogens (Fenwick 2006) and to chemical toxicants. Presently drinking water security is a global concern, and still millions of people lack daily access to clean and safe drinking water. What matters is that the water that man drinks and uses for cooking (cleaning and cooking) and for his hygiene must be drinkable, and such accomplishment requires the following properties:

> *Clearness, colorless, odorless, aerated, cooking food well, free of organic matter and substances toxic to the organism, and also free of pathogenic germs capable of causing the onset of diseases.*

In Portugal, for this purpose, the water must be treated from the physicochemical point of view, and according to the Water and Waste Services Regulatory Body (ERSAR), water must comply with the requirements set out in Table 13.1.

Other chemicals should be taken into account. For example, *fluoride* concentrations to be beneficial should be between 0.8 and 1.0 mg/L, because if they are higher than 1.0–1.5 mg/L they can cause *dental fluorosis* and *skeletal fluorosis*. Also nitrate concentrations exceeding 45 mg/L can cause health problems, particularly in children.

Aluminum (Al) is a natural constituent of many rock-forming minerals, being the most abundant metal in the Earth's crust. Also, Al is extensively found in clays, as a rule hydrous aluminum silicates and weathering products of the rock-forming minerals. Aluminum is naturally found in drinking water in the form of very fine

Table 13.1 Factors and substances that influence water potability

Substances	Maximum acceptable	Maximum admissible
Total solids	500 mg/L	1500 mg/L
Color	5 units (Pt-co)	50 units
Turbidity	5 units (UT)	50 units
Taste	Subjective limit	Subjective limit
Smell	Subjective limit	Subjective limit
Iron (Fe)	0.3 mg/L	1 mg/L
Manganese (Mn)	0.1 mg/L	0.5 mg/L
Copper (Cu)	1.0 mg/L	1.5 mg/L
Zinc (Zn)	5.0 mg/L	7.5 mg/L
Calcium (Ca)	75 mg/L	200 mg/L
Magnesium (Mg)	50 mg/L	150 mg/L
Sulfates (SO_4)	200 mg/L	400 mg/L
Chlorides (Cl)	200 mg/L	600 mg/L

clay particles suspended in the water. Aluminum is also used to improve water quality in plants doing drinking water treatment, and in some of those plants incomplete removal of Al can result in elevated Al concentrations in treated water.

Still other substances of which the following minerals are examples may also have influence on the potability of water.

Arsenic (As) also can be a contaminant of drinking water; its source includes natural weathering of minerals such as arsenopyrite (FeAsS) and pyrite (FeS_2). Arsenic's relatively high concentrations can be found in certain groundwater reservoirs. Consumption of water containing As concentrations above drinking water guidelines over long periods of time can cause a variety of health effects. The trivalent form As(III) is the most toxic, followed by the pentavalent form As(V), and then by the organic forms. The average person consumes about 10μg/day of As through water and food (particularly seafood and meat); however, As in food is usually found in the less toxic organic forms (*In*: Ritter et al. 2002).

Iron (Fe) and Manganese (Mn) are very common in drinking water, and their concentrations do not present any significant hazards to human health, but modifying the aesthetic water quality guidelines (300 and 50μg/L for Fe and Mn, respectively) is set to prevent undesirable taste and color.

These and other metals and metalloids such as lead (Pb), cadmium (Cd), mercury (Hg), selenium (Se), uranium (U), zinc (zn), and chromium (Cr) in drinking water and corresponding health effects are reported (Health Canada 1997; Ritter et al. 2002).

Guidelines on maximum recommended levels for a range of chemicals/minerals dissolved into drinking water have been developed. The maximum permissible concentrations expressed in mg/L are as follows: lead (Pb), 0.05; arsenic (As), 0.05; selenium (Se), 0.01; chromium (expressed as hexavalent Cr), 0.05; cadmium (Cd), 0.01; and barium (Ba), 2.00. For instance, *arsenic* toxicity in drinking water has been classified by the WHO as a world public health concern, in countries like Bangladesh where million people consume water from As contaminated water wells.

So far, the harmful effects of elements/minerals in drinking water are less investigated and known than the beneficial effects. Hopefully the investigation on both negative and positive effects should be carried out at the same extent. There may still be substances of an organic nature that influence the potability of water.

The treatment of water, particularly of surface reservoirs in order to make it drinkable, usually involves two operations:

1. Filtration (removal of substances in suspension by the passage of water through a filter bed of more or less fine sand)
2. Disinfection (elimination of pathogenic microorganisms by the use of chlorine (potent antiseptic, in the liquid or gaseous state)

Other operations may still take place, such as the following:

3. Coagulation-flocculation – combining the use of chemicals, for example, aluminum sulfate, to cause aggregation of colloidal particles of organic matter and clay minerals to remove color and turbidity
4. Fluoridation – to prevent tooth decay by adding fluoride in water
5. Softening – to decrease water hardness
6. Correction of aggressiveness – to correct the acidity of the water, expressed by acid pH, that is, significantly less than 7, in the sense of approaching this value

Table 13.2 shows the requirements, i.e., the guideline values and parametric values expressed in mg/L which, in 2011, by both the WHO (World Health Organization) and the EU (European Union), respectively established for water with respect to the minerals in solution. As a rule, concentrations of the so-called macrominerals or macroelements (e.g., calcium, magnesium, bicarbonate, and sulfate) are expressed in mg/L, while concentrations of the so-called microminerals or microelements (e.g., selenium, lithium, boron, and molybdenum) are expressed in µg/L.

Table 13.3 shows the range of concentrations (in mg/L) recommended for macroelements/macrominerals present in drinking water. The desirable range of pH is 7.0–8.0.

Minerals in drinking water are classified into two groups: *macrominerals* and *microminerals*, both essential to good health, naturally if they do not occur in excessive or deficient concentrations relatively to the reference concentrations.

A rather significant amount of information about the health effects of the most important macrominerals (HCO_3 or bicarbonate, SO_4 or sulfate, Cl or chloride, Ca, Mg, K, and Na) and microminerals (Fe, I, F, Mn, Li, B, Si, Cr, Se, Cu, Zn, Mo, and V) present in drinking water is currently available.

With regard to macrominerals, Rosborg and Kozisek (2015a, b) report their optimum concentrations for better protecting against diseases, as well as their functions, benefits, and risks. And, with regard to microminerals, Rosborg et al. (2015a, b) report their optimum concentrations for better protecting against diseases, as well as their functions, benefits, and risks.

Table 13.2 Guideline values and parametric values established by the WHO (2011a) and the EU (2011) for maximum concentrations of minerals present in solution in drinking water (*In*: Rosborg and Kozisek 2015a, b)

Parameters/minerals	Symbols	Guideline values, WHO	Parametric values, EU
pH	pH		6.5–9.5
Antimony	Sb	0.02 mg/L	0.005 mg/L
Aluminum	Al	0.9	0.2
Ammonium	NH_4	n.e.	0.50
Arsenic	As	0.01 (A.T)	0.01
Boron	B	2.4	1.0
Barium	Ba	0.7	n.e.
Beryllium	Be	0.012 n.e.	n.e.
Bromate	BrO_3	0.01 (A.T)	0.01
Cadmium	Cd	0.003	0.005
Cyanide	CN	0.5 n.e.	0.05
Lead	Pb	0.01 (A.T)	0.01
Chloride	Cl	250	250
Copper	Cu	2	2.0
Chromium	Cr	0.05 (P, total Cr)	0.05
Iron	Fe	2	0.2
Fluoride	F	1.5	1.5
Manganese	Mn	0.4 n.e.	0.05
Mercury	Hg	0.006	0.001
Molybdenum	Mo	0.07 n.e.	n.e.
Nickel	Ni	0.07	0.02
Nitrate	NO_3	50	50
Nitrite	NO_2	3	0.5
Selenium	Se	0.04 (P)	0.01
Sodium	Na	200	200
Sulfate	SO_4	500	250
Uranium	U	0.030 (P)	n.e.
Zinc	Zn	3	n.e.
Radioactivity		10 Bq/L, 0.1 mSv/year	0.10 mSv/year

Note: *n.e.* value not estimate or assessed, *A* provisional value, *T* provisional value, *P* provisional value

Table 13.3 shows the range of concentrations (in mg/L) recommended for macroelements/macrominerals present in drinking water, from the health point of view (Rosborg and Kozisek 2015a, b, *In*: Chapter 3 of “Drinking Water Minerals and Mineral Balance,” Rosborg I (editor), Springer).

Also, Table 13.4 contains the suggested desirable ranges for some microelements/microminerals present in drinking water from the health point of view (Rosborg, Ferrante and Soni 2015, *In*: Chapter 4 “Drinking Water Minerals and Mineral Balance,” Rosborg I (editor), Springer).

Table 13.3 Recommended concentration ranges of main *macrominerals* present in drinking water (Rosborg and Kozisek 2015a, b)

Parameters	Concentration range in mgL^{-1}
Calcium	20–80
Magnesium	10–50
Bicarbonate	100–300
Sulfate	20–250
Fluoride	0.8–1.2
TSD (total solids dissolved)	100–500

Table 13.4 Suggested desirable concentration ranges for some microelements in drinking water from the health point of view (Rosborg et al. 2015a)

Parameters	Concentration in mgL^{-1}
Boron (B)	0.1–1
Chloride (Cl)	20–100
Chromium (Cr)	0.01–0.05
Cobalt (Co)	0.005–0.02
Copper (Cu)	0.02–02
Fluoride (F)	0.8–1.2
Iodine (I)	0.005–0.075
Iron (Fe)	0.02–0.2
Lithium (Li)	0.05–0.2
Manganese (Mn)	0.02–0.05
Molybdenum (Mo)	0.005–0.02
Phosphate (PO$_4$)	0.02–0.1
Rubidium (Rb)	0.1–1
Selenium (Se)	0.005–0.05
Silicon (Si)	2–10
Vanadium (V)	0.001–0.01
Zinc (Zn)	0.02–0.2

Yet also the Table 13.5 shows the suggested safe concentration upper limits for some potentially toxic macrominerals and ions in drinking water from the health point of view (Rosborg, Soni and Kozisek 2015, *In*: Chapter 5 of "Drinking Water Minerals and Mineral Balance," Rosborg I (editor), Springer.

The book entitled *Drinking Water, Minerals and Mineral Balance: Importance, Health Significance, Safety Precautions* (editor Rosborg I 2015) presents the current knowledge of the beneficial and deleterious effects of both *macrominerals* and *microminerals* present in solution in drinking water in the health of man and other animals. Two other books dealing with drinking water should be emphasized, one entitled *Geography and Health: A Nordic Outlook* by Schaerström et al. (2014) and the other entitled *Calcium and Magnesium in Ground Water: Occurrence and Significance for Human Health* by Razowska-Jaworek (2014).

Table 13.5 Suggested safe concentration upper limits for some potentially toxic macrominerals and ions in drinking water from the health point of view (Rosborg et al. 2015b)

Parameters	Concentration in mgL^{-1}
Aluminum (Al)	<0.2
Ammonium (NH_4)	<0.5
Antimony (Sb)	<0.005
Arsenic (As)	<0.01 (0.001–0.01)
Barium (Ba)	<0.7 (0.07–0.7)
Beryllium (Be)	<0.005
Bromate (BrO_3)	<0.01
Cadmium (Cd)	<0.003
Cyanide (CN)	<0.1
Lead (Pb)	<0.01
Mercury (Hg)	<0.001
Nickel (Ni)	<0.05 (0.01–0.05)
Nitrate (NO_3)	<50
Nitrite (NO_2)	<0.5
Radioactivity	<10 Bq/L, <0.1 mSv/year
Silver (Ag)	<0.01 (0.002–0.01)
Strontium (Sr)	<0.02–0.2
Tin (Sn)	<0.1 (0.01–0.1)
Titanium (Ti)	Not set
Uranium (U)	<0.015

The function of *macrominerals* existing in drinking water (natural mineral water and spring water), and the health disorders their excess or deficiency may cause are herewith presented based on a considerable amount of currently available information; naturally the body minerals content and balance depends not only of drinking water, it also has source in dietary solid food (Burckhardt 2008; Rosborg and Kozisek 2015a, b).

Calcium (Ca^{2+}) – It is a major and vital mineral present in the generality of drinking waters. It is derived from the dissolution of Ca-bearing rock-forming minerals, such as calcite, dolomite, gypsum, calcic-sodic feldspars, pyroxenes, and amphiboles. A lifelong regular daily Ca intake is important to maintain Ca balance and healthy bone and teeth. Ca is indispensable for multiple enzymatic functions, such as cardiovascular activity, blood coagulation, and nervous system activity. Ca excess can cause coronary and vascular cerebral diseases and renal lithiasis. Ca deficiency can cause osteoporosis (Aptel et al. 1999; Bacciottini et al. 2004; Bohmer et al. 2000; EFSA 2016; Kozisek 2003; Kozisek et al. 2015; Meunier et al. 2005; Rosborg 2015; Roux et al. 2004).

Magnesium (Mg^{2+}) – It is frequent in natural mineral waters generally associated with calcium, although in relatively lower concentrations. It is derived from dissolution of Mg-bearing rock-forming minerals, magnesite, dolomite, chlorite, olivine, pyroxenes, and amphiboles. Mg is essential for a healthy life, its deficiency being responsible for muscle weakness, cramps, cardiac arrhythmia, and intestinal disorders. Mg induces the stimulation of multiple enzymatic systems and has some influence on the immune system. Mg as $MgSO_4$ can cause nausea, vomiting, and intestinal hyperactivity causing abdominal pain and diarrhea. The current RDI (recommended daily intake) for Mg is about 280–350 mg (NSFA 2012), and a higher RDI value of 450–500 mg is suggested for prevention of coronary heart disease (Altura and Altura 2009; Jiang et al. 2016).

Several studies show the association between high and low Ca and Mg contents of drinking water and human health effects (see Rosborg and Kozisek 2015a, b). Ca and Mg may act as metabolic antagonists. Kousa et al. (2006) based on a study of the diet of Finish rural population showed that high Ca and low Mg contents in drinking water significantly increases the risk of acute myocardial infarction (AMI). Durlach et al. (1989) recommend a Ca/Mg total intake ratio of 2:1.

Sodium (Na^+) – It is also a major and vital mineral in the generality of drinking water. It is derived from Na-bearing rock-forming minerals. Drinking water contains, in general, less than 20 mg/L of Na. However, for instance, in coastal areas Na content can exceed 250 mg/L due to saline intrusion and may cause high blood pressure. Na is essential for body fluid equilibrium. As aforesaid Na concentration is higher in the extracellular fluid relatively to intracellular fluid. The average of 3.3 g/day and the minimum of 500 mg/day are regarded as Na intakes for a healthy life (WHO 2011a, b). Excess of Na in extracellular fluid can cause high blood pressure, while Na deficiency may cause symptoms of nausea, vomiting, convulsion, lassitude, and muscle cramps (Bowman and Russell 2006).

Potassium (K^+) – It is common in all natural mineral waters, although in very low concentrations, as a rule within the limits 0.1–10 mg/L (Aastrup et al. 1995). It is derived from the dissolution of K-bearing rock-forming minerals, such as alkaline feldspars (microcline and orthoclase) and micas (muscovite and biotite). K together with Na is involved in maintaining the body's water balance essential in the ion exchange through cell walls, known as sodium/potassium bomb, responsible for the equilibrium of cellular osmotic pressure. About 95% of the body's K is intracellular. The recommended daily intake of K for adults is 2–4 g/day. Both excess and deficiency of K can lead to disorders in cardiac, muscle, and neurological functions (Anderson et al. 2010). Risk reducing K range has been estimated within 5–10 mg/L, and the desired Na/K ratio is 2–5:1.

Bicarbonate (HCO_3^-) – It is one of the pH regulators in the human body fluids, the carbonic acid/bicarbonate system. Generally drinking water contains 20–400 mg/L HCO_3 (Aastrup et al. 1995; Schoppen et al. 2004), and in noncarbonated water, HCO_3 concentration depends on the Ph. The highest concentration occurs at pH = 7–8 (Rosborg et al. 2003). Carbon dioxide (CO_2) is formed during carbohydrate metabolism, and its reacting with water OH produces HCO_3^- ions which are absorbed in the body fluids and contribute to pH level increase. Bicarbonate waters have this alkalinizing and antacid property; to HCO_3 is attributed the neutralization of stomach acidosis (Petraccia et al. 2006; Jones and Walter 2007). Consumption of bicarbonate water might produce significant reduction in total cholesterol (Pérez-Granados et al. 2010), and as so bicarbonate mineral water could be used in diets to reduce cardiovascular risk and prevent osteoporosis (Wynn et al. 2009a, b). Risk reducing HCO_3 range appears to be 100–300 mg/L (Rosborg and Kozisek 2015a, b).

Sulfate (SO_4^{2-}) – Sulfur participates in the synthesis of many compounds, including *chondroitin* in cartilage, bone, tendons, and blood vessels. Sulfur in natural mineral waters is associated with O in the oxidized form SO_4^{2-} or is associated with H in reduced forms HS^- e H_2S. Drinking water may contain sulfate within the range 10–500 mg/L, but higher concentrations have been reported (Aastrup et al. 1995). Sulfate in drinking water may cause peristaltism and motility in the digestive tract and the increase of secretions of the respiratory system. The reduced forms, particularly the HS^- form, are quickly absorbed both by the internal mucous membranes and by the skin. Sulfur participates in the composition of hormones, as is the case of insulin. Sulfur's reduced forms are found in sulfurous waters (Dawson et al. 2015).

On the other hand, there are *microminerals*, such as Fe, F, As, Se, Zn, Mo, Cr, Cl, P, I, etc., that at optimum low concentrations play important roles on the protection against diseases. However, like in *macrominerals*, their excess or deficiency can cause health disorders (Rosborg et al. 2015a, b).

According to the European Legislation (2009/54/EC Directive), both physical and chemical characterizations are used to make a classification of the different mineral waters, based on the analysis of main parameters (Petraccia et al. 2006).

First of all, *natural mineral waters* are classified on the basis of total dissolved solids (TDS) determined after evaporation of 1 L of water at 180 °C and expressed in mg/L. Table 13.6 shows a current TDS classification based on mineral content. By law there are no upper or lower limits for mineral content in natural mineral water; instead these limits are strictly regulated for drinking tap waters.

Total dissolved solids (TDS) is the term used to describe the total of inorganic salts and small amounts of organic matter present in solution into water. The principal constituents are usually calcium, magnesium, sodium, and potassium cations and carbonate, hydrogen carbonate, chloride, sulfate, and nitrate anions (WHO/SDE/WSH/0.3.0.4/16 2003, background document for the development of WHO Guidelines for drinking water quality). Also the presence of dissolved solids in drinking water may affect water's organoleptic properties, one being the palatability that has been rated by panels of tasters in relation to its TDS level as follows: excellent, less than 300 mg/L; good, between 300 and 600 mg/L; fair, between 600 and 900 mg/L; poor, between 900 and 1200 mg/L; and unacceptable, greater than

Table 13.6 Classification of natural mineral water based on TDS

TDS or residue at 180 °C	Definition
<50 mg/L	Very low mineral content
50–500 mg/L	Low mineral content
500–1500 mg/L	Medium mineral content
>1500 mg/L	High mineral content

1200 mg/L. Water with extremely low concentrations of TDS may also be unacceptable because of its flat, insipid taste.

The method of determining TDS in drinking water supplies most commonly used is the measurement of specific conductivity with a conductivity probe that detects the presence of ions in water. Conductivity measurements are converted into TDS values by means of a factor that changes with the type of water. The practical quantitation limit for TDS in water by this method is 10 mg/L. High TDS concentrations can also be measured gravimetrically, although volatile organic compounds are lost by this method. The constituents of TDS can also be measured individually. As far as being known, health effects associated with the ingestion of TDS in drinking water appear to exist. However, associations between various health effects and hardness, rather than TDS content, have been investigated in many studies. In early studies, inverse relationships were reported between TDS concentrations in drinking water and the incidence of cancer, coronary heart disease, arteriosclerotic heart disease, and cardiovascular disease. Also, total mortality rates were reported to be inversely correlated with TDS levels in drinking water (WHO/SDE/WSH/03.04/16 2003).

Mineral waters are also classified by other physical parameters, such as pH, temperature, hardness, alkalinity, chemical parameters, molecular concentration/osmotic pressure, and radioactivity.

With regard to pH, mineral waters are classified as *acid waters* ($pH < 7.0$), *alkaline waters* ($pH > 7.0$), and *neutral waters* ($pH = 7.0$).

With regard to water hardness, this property indicates the presence of alkaline earth metals (Ca and Mg). The hardness of mineral waters, expressed in mg$CaCO_3$/L or ppm$CaCO_3$/L, may be classified as *very soft* (0–100 mg/L of $CaCO_3$), soft (100–200 mg/L of $CaCO_3$), *hard* (200–300 mg/L of $CaCO_3$), or *very hard* (>300 mg/L of $CaCO_3$) (Albertini et al. 2007). The so-called total hardness (TH) of a mineral water is defined as the sum of the concentrations of Ca, Mg, and other multivalent cations.

Actually, in Canada, drinking water hardness is classified as *soft*, <60ppm$CaCO_3$/L; *moderately hard*, 120–60ppm$CaCO_3$/L; and *hard* >120ppm$CaCO_3$/L.

Water hardness is often expressed in °dH or "Germany degrees," where 1°dH corresponds to 10 mg/L $CaCO_3$, and water hardness classification could be as follows: very soft, 0–2°dH; soft, 2–5°dH; moderately hard, 5–10°dH; hard, 10–20°dH; and very hard, >20°dH.

Water softening filters using ion exchange resins can replace Ca and Mg ions by Na and K ions.

Mineral water alkalinity relates to the presence of bicarbonates and carbonates and other pH reactive species and, like hardness, is expressed in mg$CaCO_3$/L.

Elpiner (1995) reports the increase of *urolithiasis* frequency when groundwater with hardness higher than 10 meqL^{-1} and 300–500 mgL^{-1} of Ca is consumed. Also, several authors, such as Ortiz et al. (1990) and Yang et al. (1996) showed evidence of a correlation between coronary disease and the consumption of soft water, in particular, Mg deficient. In all the cases referred to, the authors do not explain the mechanisms of those interactions.

According to Sauvant-Rochart and Pepin (2002), a link between cardiovascular disease (CVD) mortality and the hardness of drinking water (DW) has been suggested by about 30 epidemiological studies performed worldwide in the general population since 1957. The authors make a review that examines the main ecological studies, case-control studies, and cohort studies, published between 1960 and 2000.

Very soft and acidic drinking water can be remineralized using various processes:

1. Limestone dissolution by carbon dioxide
2. Application of sodium bicarbonate, sodium sulfate, and calcium sulfate
3. Application of hydrated lime and sodium carbonate
4. Application online of micronized lime
5. Application of carbon dioxide and excess of hydrated lime (Brenner et al. 2015)

Also, very hard and alkaline drinking water can be softened using various processes:

1. Addition of lime or sodium hydroxide in order to precipitate Ca salts
2. Ion exchange resins, the Na or K ions that replace Ca and Mg ions, are released into the water
3. Ion exchange filters, using sodium chloride, the Ca and Mg ions being exchanged for Na ion (Rosborg et al. 2006)

Any of the applied treatment processes should preserve or improve as much as possible the drinking water mineral content/mineral balance (Brenner et al. 2015).

Mineral waters are also classified by chemical parameters and are named firstly by the prevalent anion and secondly by the prevalent cation.

The 2009/54/EC Directive classifies mineral waters into the following major classes:

Bicarbonate water, if bicarbonate content (CO_3H^-) is >600 mg/L; *sulfate water*, if sulfate (SO_4^{2-}) content is >200 mg/L; *chloride water*, if chloride (Cl^-) content is >200 mg/L; *fluoride water*, if fluoride (F^-) content is >1 mg/L (more than 1,5 mg/L of fluoride is unsuitable for children below the age of 7); *calcium water*, if calcium (Ca^{2+}) content is >150 mg/L; *magnesium water*, if magnesium (Mg^{2+}) content is >50 mg/L; and *sodium water*, if sodium (Na^+) content is >200 mg/L.

The significant number of clinical studies being carried out so far have provided much information on the mineral medicinal properties of specific natural mineral waters, and about this subject, the article of Quattrini et al. (2016) is an interesting review, and in a very synthetic way, the following notes are below reproduced:

Bicarbonate or bicarbonated mineral waters can provide positive effects on the digestive tract. Studies on crenotherapy treatments and on patients with functional dyspepsia show that the consumption of bicarbonate mineral water may neutralize acid secretion, increase the pH level in the gastric lumen, accelerate gastric emptying, and stimulate the release of digestive hormones, known to have pivotal roles in the regulation of gastric function (Capurso et al. 1999; Bertoni et al. 2002).

Sulfate or sulfated mineral waters are characterized by the presence of sulfate anion associated with cations such as Ca, Mg, and Na, and these cations could provide and enhance water specific properties: magnesium sulfate and sodium sulfate mineral waters demonstrated to be really efficient for functional constipation conditions (Dupont et al. 2014). Drinking mineral water rich in magnesium sulfate and sodium sulfate can confer significant benefits for healthy digestion, in terms of improvement of constipation symptoms, overall bowel movements, and stool consistency (Bothe et al. 2015). Sulfate waters, those that contain sulfate ion (SO_4^{2-}), are balneotherapeutically used mainly in the management of gastrohepatological and biliary conditions in the form of balneological drinking cures or hydropinic therapies (Fraioli et al. 2010; Mennuni et al. 2014; Bothe et al. 2015).

In mineral waters sulfur can occur too as sulfate ion SO_4^{2-} or as hydrogen sulfide gas (H_2S). Drinking of H_2S waters is not common, particularly due to their unpleasant taste and smell, the "rotten egg" smell.

Hydrogen sulfide (H_2S) waters, also called "sulfur waters" and sulfurous waters, are applied mostly in the form of baths defined as H_2S or sulfur balneotherapy and indicated most frequently in the management of rheumatic diseases (Karagülle et al. 1996; Ekmekcioglu et al. 2002; Leibetseder et al. 2004) and a lesser extent in dermatological conditions (Costantino et al. 2005; Huang et al. 2018; Carbajo et al. 2018).

Balneological waters classified as sulfate waters are defined as those containing at least 1200 mg/L sulfate (SO_4^{2-}); the ones originally and naturally containing dissolved H_2S gas with an S^{2-} level at least 1 mg/L are named "sulfur waters" (Karagülle and Dönmez 2002; Karagülle and Karagülle 2019).

Karagülle and Karagülle (2019) report a systematic review aimed to evaluate in vivo experimental studies investigating the biological effects of natural H_2S water drinking in healthy and ill model laboratory animals. The studies have indicated several health effects in mice. The authors question if the in vivo-obtained benefits of biological parameters would exert similar effects on humans undergoing traditional hydroponic therapies or drinking cures with H_2S waters at natural sulfur water spas/health resorts or natural (even artificial) H_2S water consumption at home and conclude that the question would be clarified by clinical trials.

Chloride or chlorinated mineral waters are composed by chloride as predominant element and the most abundant cations are sodium, calcium, and magnesium. Although studies about their health effects are scarce, chloride mineral water may exert their properties for bowel functions: they may stimulate intestinal peristalsis and intestinal secretion of water and electrolytes (Petraccia et al. 2006). Moreover, they may have a choleretic and cholagogue action by increasing biliary secretion and bile inflow into the duodenum (Casado et al. 2015).

Fluoride or fluoridated mineral waters are indicated for children, because they can reduce the incidence of decay and promote bone mineralization. However, high

> fluoride consumption may have some toxic effects, from dental fluorosis to skeletal fluorosis, if fluoride intake is above 10 mg/L. For this reason, the European Food Safety Agency (EFSA) established fluoride upper limit of exposure to 1.5 mg/L/day (EFSA 2005), a limit that was also confirmed by the World Health Organization (WHO 2011a, b).

It is well established and recognized that minerals are more easily absorbed in the gut if they come from water than from food. Several interesting topics are covered in the book. One of them is the possibility of negative interaction between certain minerals present in the water, as is the case of the antagonistic Ca/Mg interaction. When Ca, essential mineral for the formation of healthy bones and teeth, is in excess in water, this may counteract the incorporation of Mg, essential for a healthy heart. Therefore, an optimum balance between the two minerals present in drinking water is fundamental. The ideal Ca/Mg ratio lies in the range 2–3:1.

The concentration levels of chemical constituents (macroelements as well as microelements, toxic elements included) of certain water, that is, its hydrogeochemical signature, determines water potability and its use in agriculture, recreation, and health and the interactions with biological systems (Zhu and Schwartz 2011).

The negative correlation between the chemistry of drinking water supplies in a certain area and the incidence of cardiovascular disease among the people living in that area has been reported (Crawford et al. 1997; Comstock 1979; Bernardi et al. 1995). Although not being a proven causation, the impact of the inorganic chemistry of the groundwater on cardiovascular diseases has puzzled many researchers (Dissanayake and Chandrajith 2006). Various scientific studies show that hard water bearing high concentrations of Ca, Mg, HCO_3, and SO_4 is protective against cardiovascular diseases. Such correlation has been observed in many countries and in many regions or areas (Dissanayake and Chandrajith 1999), and it has been suggested the Mg present in abundance in the hard water may well be the factor showing cardioprotective influence (Marier 1968; Anderson 1972; Altura and Altura 1991; Rubenowitz et al. 2000).

In Canada, from a survey of 15 elements in 575 drinking water, Neri et al. (1975, 1977) have concluded that Mg is the most likely element that is responsible for the protective cardiovascular effect. The authors based such conclusion on the following facts:

1. Mg was present in more than 10% of the sample waters.
2. Mg is a consistent function of the softness-hardness gradient.
3. Mg represents a significantly high proportion of the daily intake from other sources.
4. The known metabolic effects of Mg are consistent with the hardness-mortality trend.

Since the crustal concentration of Mg is much lower than that of Ca, Mg is found in lower concentrations in natural waters with an average Ca/Mg ratio of 4. According to Kozisek (2003), Mg deficiency is known to be linked to vasoconstrictions, hypertension, cardiac arrhythmia, and acute myocardial infarction, among other

Table 13.7 Suggested concentration ranges for some mineral ratios in drinking water from the health point of view (*In*: Rosborg and Kozisek 2015a, b)

Mineral ratios	Safe conc. range	
Ca/Mg	2–3:1	
Na/Mg	3–4:1	Na < 100 mg/L
Na/Ca	1–3:1	Na < 100 mg/L
Na/K	2–5:1	Na < 100 mg/L
$(Mg + SO_4)$	100–400	Mg < 150 mg/L
$(Ca + Mg + Na + K) = (SO_4 + CO_3 + HCO_3 + Cl)$	Ion balance	Meq/L

cardiovascular diseases. Marier (1978) reported from an analysis of 350 tissue samples from 161 autopsy cases observed that myocardial Mg was 6% lower in “cardiac death” patients from soft water localities in comparison with hard water regions.

The ion balance is an important factor used to check water chemical analytical data. The sum of the anion concentrations should be equal to the sum of cation concentrations.

Table 13.7 shows the desirable concentration ranges for some mineral ratios in drinking water from the health point of view.

In Portugal each citizen spends, on average, 168 liters of water per day. In the country, 926,923m^3/year (34% from boreholes and 66% from dams) are collected, and of the 823,291m^3 of treated water, 693,074m^3 are distributed by consumers, 594,393m^3 for domestic consumption, and the remainder for other uses.

Man has also used water for drinking and for agricultural and industrial purposes, since the earliest civilizations, for hygienic and sanitary purposes. The last two applications referred to degrade the quality of effluent water that is fed into rivers, lakes, seas, and oceans. The microbiological quality of drinking water is inherently linked to sanitary practices, with fecal pathogenic microorganisms being the most common source of contamination.

The filtration of water by the soil and sediments of the aquifers, more efficient when the soils and sediments contain a significant amount of clay (whose micrometric dimension and electric charge favor the fixation of inorganic and organic contaminants), can provide natural protection against the said microorganisms, which is why water from underground aquifers is the most attractive option for the safe consumption of drinking water.

The water circulating through the rocks extracts from them by chemical dissolution of the minerals which in this case are chemical elements in the ionic form, such as sodium, potassium, calcium, magnesium, iron, silicon, aluminum, etc., and the foregoing properties may provide therapeutic benefits or simply effects favorable to human health. However, the chemical dissolution of certain minerals, usually sulfides, can lead to the concentration of toxic chemical elements, such as arsenic (As) and lead (Pb), in aquifers and their contamination, with serious consequences for human health.

An example of this is the arsenic contamination of water used for human consumption from shallow wells in Bangladesh and South India (Charlet and Polya 2006; Polya and Charlet 2009). In Bangladesh alone, arsenic-contaminated groundwater affects between 35 and 75 million people (Chen et al. 2009). More than 95% of the population now uses groundwater from about 10 (ten) million tube wells, and about 60% of these wells along the Ganges-Brahmaputra river system in Bangladesh are affected by As levels exceeding the WHO limit (Ahmed et al. 2004). Arsenic pollution is also of concern in other parts of the world.

About 6 (six) million people are at risk in West Bengal in India (Haque et al. 2003).

High concentrations of arsenic, adsorbed on iron oxides and hydroxides, occur naturally in the sediments of the Ganges Delta, and anthropogenic processes led to the mobilization of arsenic into almost superficial aquifers. About 20 (twenty) million people consume water contaminated with As, and their health is exposed to serious concerns. Chronic As poisoning leads to As accumulation in the skin, hair, and nails, an accumulation that results in symptoms such as strong pigmentation of hands and feet (keratosis), high blood pressure, and neurological dysfunctions (Chen et al. 2009).

The maximum levels of arsenic (the primary sources of which may be natural or anthropogenic, in this case from industrial pollution) and lead contamination (the primary sources of which are fuel, paint, and metal according to the WHO (World Health Organization), that could be present in water for human consumption are 0.01 mg/L and 0.01 mg/L, respectively.

In Portugal, for instance, relatively high concentrations of arsenic have been reported in some villages where the supply is made from groundwater abstractions that travel through fractures filled with arsenic-bearing sulfides, such as *arsenopyrite* (FeAsS) and *arsenic pyrite* (FeS_2). Anomalous levels of arsenic have been reported in waters consumed in certain places in the municipalities of Baião, Valbom, Vila Flor, and Ponte de Sor.

A note on the interaction of water/minerals to which there may be associated danger to ecosystems and to human health, for example the interaction of the waste or bargain of mining activity deposited and accumulated in so-called mine wastes located in the vicinity of the mines. Hazard can be particularly serious when mines are either deactivated or abandoned. Such wastes which are solid and liquid by-products from mining, mineral processing, and metallurgical extraction, as a rule, have no economic value. In many situations the residues of the mines being exposed to the atmosphere, hydrosphere, and microorganism conditions generate acidic effluents with high concentration of sulfate and metals (when the residues contain sulfides, the pH can show values of 3–5) or alternatively alkaline, metal, and metalloid solutions (Fe, Al, Cu, Zn, Cd, Pb, Ni, Co, Cr, As, Sb, Mo, U, and F) potentially toxic to humans and ecosystems when discharges rivers, lakes, and oceans (Hudson-Edwards et al. 2011; Nordstrom 2011).

Plumlee and Morman (2011) discuss the factors influencing the effects on human health of "mine wastes," in particular lead, mercury, and arsenic.

It should be noted that the extractive industry can have a strong impact on water quality and, consequently, on human health. Effectively, the process of remobilization of the mineralized geological materials and the concentration of the useful minerals is often by the action of the water that, of course, can by chemical leaching and dissolution start to include potentially toxic and polluting chemical elements for the ecosystems and indirectly for the man's health. Also, the use of fertilizers and pesticides in agriculture is a source of pollution of surface water and groundwater.

Nitrates, whose primary source is agricultural activity, are another possible contaminant of water for human consumption. The maximum levels of nitrate contamination allowed by both the EU (European Union) and the WHO (World Health Organization) are 50 mg/L. Also, phosphates, whose primary sources are the agrochemicals, are another possible contaminant.

About half of the world's population has water shortages and is confronted with water quality issues from vulnerable resources such as rivers, lakes, ponds, and shallow wells (WHO/UNICEF 2010).

A recognized international specialist in groundwater, the Spanish Ramon Llamas (2015), considers water scarcity today as a myth and criticizes the "hydrosquizophrenia" that prevails in many countries and for which there is still no known cure. According to Ramón Llamas, the problem lies in the mismanagement of aquifers and the inefficient use of water in unprofitable economic activities, such as irrigation of low-value agricultural products, warns the expert on the political use of water, and he states that the desalination of seawater has been a failure from the point of view of its agricultural use, when in many coastal regions the desalinated water could be used preferentially to groundwater. This is not only because the unit cost of desalinated water is significantly higher than the cost of groundwater, whose quality is degraded by the use of agrochemicals (fertilizers, insecticides, and fungicides), marine intrusion, etc. Ramón Llamas also states that the failure of construction in Spain of 20 (twenty) desalination plants whose water would be for agricultural use was due to the high cost of water for this purpose. However, the cost of desalinated water is already bearable when the goal is urban use.

The worldwide shortage of water for human consumption could be balanced by demineralization/desalinization of seawater and brackish water using the process called reverse osmosis that unlike natural osmosis requires the input of an external pressure to drive the water flow in the opposite direction (Crittenden et al. 2012).

In Portugal 594 million m^3 of drinking water is produced for consumption, and 13,782 km of pipelines are installed to transport this water. In 2016, ERSAR (the Portuguese Water and Waste Services Regulatory Body) estimated that 243,017 homes on the mainland are not connected to public water supply networks and use alternative sources of water supply, wells, and bottled water.

The coverage rate, i.e., the water from the public water supply arriving at homes, was estimated at 96%, and the coverage rate for wastewater treatment was estimated at 83%. Bringing piped water to small, widely dispersed settlements in the territory is difficult and very expensive. The water pipes for public supply then comprised 100,000 km.

Of course, these alternative sources may involve health risks due to possible microbiological contamination and chemical contamination; this is linked to the use of pesticides and fertilizers in agricultural practices, in the last case of nitrogenous and phosphate nature, and also to the presence of heavy metals. In these cases, the control of water quality is the responsibility of the consumer, whereby such control may not exist. Periodic analyses should be done to avoid exposure to contamination.

There are diseases that are associated with lack of drinking water quality, such as hepatitis A and B and typhoid fever.

Water disinfection is an issue of paramount importance in terms of public health, since most of outbreaks of disease come as a result of water- and food-borne enteric bacteria. Among them, typhoid and food poisoning (*Salmonella typhi*), dysentery and diarrhea (*Escherichia coli*), and cholera (*Vibrio cholera*) are enhanced. The virulence of these pathogens is so high that it is one of the main sources of death in the developing world. Thus, it has been reported that worldwide 1.3 million deaths of children are attributed to diarrheal illness each year.

According to the Portuguese DGS (General Directorate of Health) in 2012, only 10 cases of hepatitis A were registered, when in 1980 3000 cases were diagnosed. From a bacteriological point of view, the treated water should not contain coliform bacteria as is the case of enteric bacterium *E. coli* whose presence is indicative of fecal contamination, and the index NMP (most likely number of pathogenic microorganisms present in 100 ml water) should be less than 1.

Water must be made safe to drink, and an important step in ensuring water safety is disinfection. Disinfectants are added to water to kill disease-causing microorganisms. Groundwater sources can be disinfected by “The Water Treatment Rule,” which requires public water systems for disinfection. Chlorination, ozone, ultraviolet light, and chloramines are primary methods for disinfection (Ishaq et al. 2018).

The EPA (Environmental Protection Agency) of the USA established in “The Water Treatment Rule” the minimum treatment requirements for public water systems using surface water as supply sources. Actually, chlorine is the most used chemical agent for water disinfection due to its low cost, effectiveness, and their extra protection against regrowth of pathogens and bacteria (Amin et al. 2014). Nevertheless, chlorine has received negative publicity, mainly due to the discovery that chlorination of water containing organic compounds could lead to the formation of trihalomethanes (THMs), which are suspected of having detrimental health effects (Nieuwenhuijsen et al. 2009; Villanueva et al. 2007).

On the other hand, some microorganisms have developed a special chlorine-induced antibiotic resistance in such a way that high dosage of the disinfectant in the water treatment is required (Yuan et al. 2015). Ozone and the use of membranes filters (Wang et al. 2015; Nassar et al. 2012) are alternative methods. The adsorption technique is the most sustainable alternative to the chemical agents to remove pathogens from potable water and wastewater due to its high simplicity, low-cost operation, high efficiency, as well as ease of regeneration. Among the adsorbents developed in recent years, *hydrotalcites* (Jin et al. 2007), metallic nanoparticles (Deng et al. 2014), have emerged as potential alternatives to chlorine for the removal of pathogenic organisms from water.

Pichel et al. (2019) present an interesting review on the conventional technologies being applied at medium to large scales to purify water and emerging technologies currently in development. The authors describe the merits, demerits, and limitations of the technologies, and they put a particular focus on solar disinfection, including a novel technology recently developed in this field.

In Europe water is considered "safe water" if it is monitored in line with European standards and whose analytical results meet the limits imposed. In the mainland of Portugal, ERSAR is responsible for regulating and supervising the quality of water for human consumption.

As in minerals *strictu sensu* or minerals *s.s*, in general, there are no two natural mineral waters alike with each water having a genetic signature or DNA, depending on its hydrobiochemochemical composition. Today, the chemical, physical, or physicochemical properties of natural mineral waters are relatively well known, as is not the case with a microbiological component also called *microbiota* or *microbiome*. In the microbiological component, only the pathogenic microorganisms (due to the negative impacts they have on human health) have been studied. The other microorganisms and their metabolites can be factors justifying the therapeutic properties of mineromedicinal mineral waters. The *microbio*ta of a natural mineral water is the bacterial, pathogenic, and nonpathogenic flora, which is very constant, which contains, at the outlet of the spring, flora whose qualitative and quantitative composition must be controlled through periodic analyzes (Directive 2009/54/EC).

The spring waters certified as *bacteriologically pure* are considered to be best termed as *pathogen germ-free* waters. Even so, several bacterial species can be identified by genomic sequential analysis. The overall nonpathogenic bacterial populations of one spring water, comprehensively termed microbiota, may be responsible for its regenerative properties. These properties may be related to the production of so far unknown substances that promote regeneration, probably in synergy with macro- and micromineral elements of the spring water (Pellegatta et al. 2016). The role of microbiota in controlling the balance between health and disease is a current topic of study due to its potential to be used for novel therapeutic approaches (Belizário and Napolitano 2015).

Nicolleti et al. (2017) have confirmed the ex vivo regenerative effects of a spring water, in a human ex vivo experimental model in the context of physiological wound healing using filtered Comano spring water in Italy. Previous experiments have indicated that the Italian calcium magnesium bicarbonate-based Comano spring water improves skin regeneration which was possibly associated with the native nonpathogenic bacterial flora (Faga et al. 2012).

The use of *natural mineral water*, *associated natural resources*, and *thermal tourism* are important contributions to the economy of the region where the *natural mineral water* occurs.

As has been aforesaid, *spring water* is a water of underground circulation and bacteriologically appropriate in its natural state for human consumption or health care. In Portugal, *spring water*s belong to the private domain, its use requiring an exploitation license issued by the local and regional administration.

With regard to *natural mineral waters* and *spring waters*, Portugal has a large diversity of waters, still (i.e., without natural gas), gasocarbon (i.e., bearing gas, CO_2, natural), and carbonated (i.e., bearing gas CO_2, artificial), which are marketed bottled.

Already in 1930, the eminent chemist Charles Lepierre in his book "Chimie et Physico-Chimie des Eaux (Le Portugal Hydrologique et Climatic)" said:

> Portugal, in proportion to its surface area and its population, is one of the richest countries in the world, in what concerns the variety and number of its mineral water springs.

In continental or mainland Portugal, 33 (thirty-three) brands of mineral water are known for bottling, marketing, and drinking, 18 (eighteen) classified as *natural mineral water*, and 15 (fifteen) classified as *spring water*. Among the bottled still *natural mineral waters*, the following stand out: Alardo, Fastio, São Cristovão, Vitalis, Luso, Penacova, and Monchique. Also, among the still flowing *spring waters*, the following stand out: Caramulo, Cruzeiro, Glaciar, Serra da Estrela, and Serrana. In addition, within the natural gas-rich mineral waters, the water of Pedras Salgadas stands out; the carbon dioxide it contains is 100% natural. Pedras Salgadas (Pedras Salgadas-Vila Pouca de Aguiar) is a singular natural mineral water classified as sodium bicarbonate water, HCO_3, Na, and DR (dry residue determined at 180 °C) contents being 1983 mg/L, 577 mg/L, and 2807 mg/L, respectively, and it is a current suitable drink to be taken after a substantial meal. The so-called carbonated waters are those to which carbon dioxide of origin other than the carbonic gas of the aquifer from which the water is supplied has been added.

The bottles of all bottled waters should show a label that allows the consumers to have enough information to know the physicochemical characteristics of the water they will ingest. The most relevant physical and chemical parameters (pH, total mineralization, and total dissolved salts) and the contents of the main anions and cations of the water should be indicated on the bottle label in addition to the commercial name, place of exploitation, and name of the source where it was extracted.

Bottled drinking water, both natural mineral water and spring water, has to be "clearness or limpidness, odorless, tasteless, colorless and harmless, that is devoid of pathogenic microorganisms and harmful chemicals to humans" and "safe" on the basis of established microbiological, physical, and chemical parameters (Quattrini et al. 2016).

The book *Geochemistry of Europa Bottled Water* published in 2010 by Borntrager Science, by Stuttgart, Reimann C, and Birke M (eds.), was the first state-of-the-art overview of the chemistry of groundwaters from 40 (forty) European countries from Portugal to Russia, measured on 1785 bottled water samples from 1247 wells representing 884 locations plus additional 500 tap water samples acquired in 2008 by the network of EuroGeoSurveys experts all across Europe. The book presents a comprehensive internally consistent overview of the natural distribution and variation of the determined chemical elements and additional state parameters of groundwater at the European scale. Most elements show a very wide range – usually 3–4 but up to 7 orders of magnitude – of natural variation of their concentration. Data are interpreted in terms of their origin, considering hydrochemical parameters, such as the influence of soil, vegetation cover, and mixing with deep waters, as well as other factors (bottling effects, leaching from bottles). The authors also provide an overview of the legal framework, that any bottled water sold in the European Union must comply with. It includes a comprehensive compilation of current drinking water action levels in European countries, limiting values of the European Drinking/Mineral/Natural Mineral Water directives (1998/83/EC, 2003/40/EC, 2009/54/EC), and legislation in effect in 26 individual European countries, and for comparison those of the FAO, and in effect in the USA (EPA, maximum contaminant levels [MCA]).

In recent times many studies have focused attention on the safety of bottled mineral water, in particular on the migration of chemicals from plastic containers to water. Plasticizers (additives used to impart flexibility and handling properties to several kinds of plastics) and *endocrine disruptors* (Eds – chemicals that interfere with function of the endocrine system) (Pinto and Reali 2009) are the main compounds involved in adverse effects on human health. Among these are the plasticizers like the Di(2-ethylhexyl)phthalate (DEHP) that is widely used as plasticizer and is also present in PET bottles (Bosnir et al. 2003). Polyethylene terephthalate (PET) is a material chemical inactive, but some in vitro studies proved that storage conditions (like exposure to sunlight and high temperature) may contribute to the release of chemicals from bottles to water (Biscardi et al. 2003).

The consumption of bottled mineral waters has greatly increased during the past few years, worldwide. The consumption of bottled water has been increasing all over the world. In Portugal, currently, the statistical data point to the consumption of 110 liters/inhabitant/year. And, about 57 (fifty-seven) million liters are exported, with Angola being the largest market. The bottled waters comprise natural mineral waters and spring waters, contributing the first with about 210 (two hundred ten) million euros for the national economy, with the second contributing with about 60 (sixty) million euros.

13.4 Water as an Essential Constituent of the Human Body and as a Health Conditioner

13.4.1 Basic Information

Water contributes significantly to health and good health, and is the essence of development. However, water's protective role is largely unseen and taken for granted in the wealthier countries. Its contribution to health is directly within households through food and nutrition and indirectly as a means of maintaining a healthy, diverse environment. These two precious resources – water and health – together could enhance prospects for development.

In humans, about 70% of body weight is represented by total body water (TBW), distributed into intracellular and extracellular fluid compartments, which contain about 65% and 35% of total body water, respectively.

Water is involved in many bodily functions, since it serves as a carrier of nutrients and substances in the circulatory system. Furthermore, water is the vehicle to excrete products and eliminate waste and toxins, and it also lubricates and provides structural supports to tissues and joints. However, there is no efficient mechanism for the body's water storage; therefore, a constant supply of fluids is needed to maintain water content. Water is present in all cells of the human body (in addition to water, cells also contain proteins, carbohydrates, lipids, and other compounds), in the intercellular fluid and also in the so-called organic fluids (blood plasma, urine, lymph, etc.). Water is the main vehicle for transporting nutrients and other substances into the circulatory system and is also the vehicle for the elimination of metabolites and toxins through the vascular, renal, and hepatic systems.

Table 13.8 Concentrations of minerals in the blood serum and in the human body (Peacock (2010); Bloodbook (2013); FNB (2005); Abramowitz et al. (2012); Bowman and Russell (2006); NSFA (2013); Deng et al. (2008); Wallach (2007), (*In*: Ferrante et al. 2015))

Minerals	Normal range of concentrations in serum	Total content in human body	RDD
Calcium (Ca)	8.8–10.4 mg/dL	1000–1200 g	1000 mg
Magnesium (Mg)	3.7–4.9 mg/dL	25–30 g	300
Bicarbonate (HCO_3)	110–140 mg/dL		
Sulfate (SO_4)	27–30 mg/dL		
Sodium (Na)	331–335 mg/dL	90–100 g	<2 g (0.18 g minimum required)
Potassium (K)	13.7–19.6 mg/dL	140–225 g	3 g
Phosphorous (P)	3.0–4.5 mg/dL	750–850 g	700 mg
Chloride (Cl)	350–376 mg/dL	82 g	<3 g
Iron (Fe)		2.1–2.8 g	12 mg
Copper (Cu)	70–150μg/dL	70–80 mg	0.8 mg
Molybdenum (Mo)			45μg
Zinc (Zn)	0.06–0.12 mg/dL	1.5–2.5 g	8 mg
Chromium (Cr)	5–55μg/dL	6 mg	100μg
pH	7.34–7.45		
Ca/Mg	2.1–3.1:1		3:1
Na/Ca	32–35:1		2:1
Na/K	20–40:1		0.67:1
Ca/P	2.3–8.5:1		1.4:1
Na/Mg	68–84:1		0.6 (min.)–7:1
(Na + K)/(Cl + HCO_3)	3.0–11:1		

Table 13.9 Percentage by weight and volume of water in the major body tissues of an adult weighing 70 kg (*In*: Failde 2008a, b)

Tissue	Water (%)	Water (L)
Kidney	83	0.25
Lung	80	0.40
Blood	76	4.65
Cerebrum	75	1
Muscle	76	22.10
Skin	72	10
Bone	22	2.45

Table 13.10 Chemical composition of intracellular and extracellular liquids

Elements/compounds	Intracellular liquid	Extracellular liquid
Sodium	10 mmol/L	142 mmol/L
Potassium	156	4
Calcium	3	5
Magnesium	26	2
Total	**195** mmol/L	**153** mmol/L
Chlorine	2 mmol/L	103 mmol/L
Bicarbonate	8	26
Phosphate	95	2
Organic acids	>20	6
Proteins	55	16
Total	**>180** mmol/L	**153** mmol/L

About 70% by weight of the human body consists of water, and there are organs that contain more water than others. In a man weighing 65–70 kg, there are 40 to 42 (forty to forty-two) liters of water, about 25 (twenty-five) liters inside the cells, called intracellular water, and about 17 (seventeen) liters on the outside of the cells, called extracellular water, which comprises about 13 (thirteen) liters of the so-called interstitial water and about 4 liters of the so-called intravascular water.

In intravascular water, in the case of blood, it contains about 90% of water, mainly in blood plasma, which in addition to water contains red blood cells and white blood cells, platelets, minerals (Na, K, Ca, Mg, Zn, Cr, P, etc.), proteins, and glucose.

Minerals are important constituents of both water and the human body. In this, in quantitative terms, the total of minerals corresponds to about 5% of the mass of the human body. Table 13.8 shows the ranges of total concentrations of the major minerals in the human body, the range of concentrations of the major minerals in the blood serum, and the recommended daily dose (RDD) or recommended daily intake (RDI) values for an adult with the weight of 70 kg.

Table 13.9 shows the percentage by weight and volume of water contained in the main tissues of an adult body weighing 70 kg.

Men's body has about 15% more water than women's body. And, from the relative point of view, it is in the body of the newly born baby that the water content is higher (estimated at about 90%). Intracellular and extracellular water or body fluids have distinct compositions and concentrations in terms of cations, anions, and other dissolved compounds. According to Teixeira (2009), cell membranes are fundamentally responsible for regulating and controlling ion exchange between *extracellular* and *intracellular* fluids.

Table 13.10 shows the concentrations in millimoles per liter (mmol/L) of the major cations and anions of body waters.

A state of good health requires intracellular water and extracellular water to be more or less in dynamic equilibrium; the same must occur with chemical elements and compounds, that is, the search for electrolyte equilibrium.

An active adult requires about 30–35 ml/kg/day (milliliters per kilo per day) of water, meaning that an adult weighing 70 kg should drink a little more than 2 L/day. In a normal diet, of the total water intake, 20–25% comes from solid foods and 75–80% comes from liquid foods.

The lack of water in the human body can lead to dehydration. Signs of dehydration can be classified into two types: mild or moderate (drowsiness and tiredness, headache, dizziness, dry mouth, thirst, muscle weakness, and decreased urine production) and severe (severe drowsiness, irritability, fever, dry mouth, dry skin, very dry mucous membranes, extreme thirst, tachycardia, lack of sweating, i.e., sweat production, and little or none in urine). Even if you are not thirsty, it is essential to drink water to meet the hydration needs that increase with the heat because the body loses more water in the mechanisms of counter-regulation of body temperature.

Under normal conditions, body water volume may fluctuate less than 1% per day. A state of dehydration due to losses equal to or greater than 2% of body water volume may result in impairment of cognitive function, physical performance, and fatigue symptoms.

References

Aastrup M, Thunholm B, Johnson J, Bertills U, Berntell A (1995) The chemistry of ground water. The Swedish bed-rock. SEPA report 4415

Abramowitz MK, Hostetter T, Melamed ML (2012) Lower serum bicarbonate and a higher anion gap are associated with lower cardiorespiratory fitness in young adults. Kidney Int 81(10):1033–1042

Ahmed KM, Bhattacharya P, Hasan MA, Akhter SH, Alam SMM et al (2004) Arsenic enrichment in groundwater of the alluvial aquifers in Bangladesh: an overview. Appl Geochem 19:181–200

Albertini MC, Dacha M, Teodori L, Conti ME (2007) Drinking mineral waters: biochemical effects and health implications – the state-of-the-art. Int J Environmental Health 1(1)

Altura BM, Altura BT (1991) Cardiovascular risk factors and magnesium: relationships to atherosclerosis, ischemic heart disease and hypertension. Magnes Trace Elem 10:182–192

Altura BM, Altura BT (2009) Atherosclerosis and magnesium, in calcium and magnesium in drinking water: public health significance. World Health Organization, Geneva, pp 77–83

Amin MT, Alazba AA, Manzoor U (2014) A review of removal of pollutants from water/wastewater using different types of nanomaterials. Adv Mat Sci Eng 2014

Anderson TW (1972) Can water cause heart disease? Proceedings of the 6th international water quality symposium April 18–19, 28–31, Washington DC

Anderson J, Young L, Long E (2010) K and health. Colorado State University. http://www.american-heart.org/presenter.jhtml?identifier=4680

Aptel I, Cance-Rouzaud A, Grandjean H (1999) Association between calcium ingested from drinking water and femoral bone density in elderly women: evidence from the EPIDOS cohort. J Bone Miner Res 14(5):829–833

Bacciottini L, Tanini A, Falchetti A, Masi L, Franceschelli F, Pampaloni B, Giorgi G, Brandi ML (2004) Calcium bioavailability from a calcium-rich mineral water, with some observations on method. J Clin Gastroenterol 38(9):761–766

Belizário JE, Napolitano M (2015) Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. Front Microbiol 6:1050

Bernardi D, Dini FL, Azzrelli A, Giaconi A, Volterrani C, Lunardi M (1995) Sudden cardiac death rate in an area characterized by high incidence of coronary artery disease and low hardness of drinking water. Angiology 46:145–149

Bertoni M, Olivieri F, Manghetti M, Boccolini E, Bellomini MG, Blandizzi C, Bonino F, Del Tacca M (2002) Effects of a bicarbonate-alkaline mineral water on gastric functions and functional dyspepsia: a preclinical and clinical study. Pharmacol Res 46(6):525–531

Biscardi D, Monarca S, De Fusco R, Senatore F, Poli P, Buschini A, Rossi C, Zani C (2003) Evaluation of the migration of mutagens/carcinogens from PET bottles into mineral water by Tradescantia/micronuclei test, Comet assay on leukocytes and GC/MS. Sci Total Environ 302(1–3):101–108

Bloodbook (2013). http://www.bloodbook.com/ranges.html#Potassium

FNB, Food and Nutrition Board (2005) Dietary reference intakes for water, K, Na, chloride, and sulfate. National Academies Press, Washington, DC

Bohmer H, Muller H, Resch KL (2000) Calcium supplementation with calcium-rich mineral waters: a systematic review and meta-analysis of its bioavailability. Osteoporos Int 11(11):938–943

Bosnir J, Puntarić D, Skes I, Klarić M, Simić S, Zorić I (2003) Migration of phthalates from plastic products to model solutions. Coll Antropol 27(Suppl 1):23–30

Bothe G, Coh A, Auinger A (2015) Efficacy and safety of a natural mineral water rich in magnesium and sulphate for bowel function: a doubleblind, randomized, placebo-controlled study. Eur J Nutr 18

Bowman BA, Russell RM (2006) Nutrition, v.1, 9th ed. ILSI, International Life Sciences Institute, Washington, DC

Brenner A, Persson KM, Russell L, Rosborg I, Kozisek F (2015) Technical and mineral level effects of water treatment. In: Rosborg I (ed) Drinking water minerals and mineral balance: importance, health significance, safety precautions. Chapter 6. Springer, pp 103–117

Burckhardt P (2008) The effect of the alkali load of mineral water on bone metabolism: interventional studies. J Nutr 138(2):435S–437S

Capurso A, Solfrizzi V, Panza F, Mastroianni F, Torres F, Del Parigi A, Colacicco AM, Capurso C, Nicoletti G, Veneziani B, Cellamare S, Scalabrino A (1999) Increased bile acid excretion and reduction of serum cholesterol after crenotherapy with saltrich mineral water. Aging (Milano) 11(4):273–276

Carbajo JM, Ubogui J, Vela L, Maraver F (2018) Sulphurous minerals waters and psoriasis. Med Nat 12:58–602

Casado Á, Ramos P, Rodríguez J, Moreno N, Gil P (2015) Types and characteristics of drinking water for hydration in the elderly. Crit Rev Food Sci Nutr. 55(12), 1633-1641

Rosborg I (ed) (2015) Chapter 3 of the book Drinking water minerals and mineral balance: importance, health significance, saftey precautions. Springer International Publishing, Cham, pp 33–52

Charlet L, Polya D (2006) Arsenic in shallow reducing groundwaters in southern Asia: an environmental health disaster. Elements 2:91–96

Chen Y, Parvez F, Gamble M, Islam T, Ahmed A et al (2009) Arsenic exposure at low-to-moderate levels and skin lesions, arsenic metabolism, neurological functions, and biomarkers for respiratory and cardiovascular diseases: review of recent findings from the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh. Toxicol Appl Pharmacol 239:184–192

Comstock GW (1979) Water hardness and cardiovascular diseases. Am J Epidemiol 110:375–400

Costantino M, Nappi G, Contaldi E, Lampa E (2005) Effectiveness of sulphur spa therapy in psoriasis: clinical-experimental study. Med Clin Term 18:127–137

Crawford MD, Clayton DG, Stanley F, Smkpfr AG (1997) An epidemiological study of sudden death in hard and soft water areas. J Chron Diseases 30:69–80

Crittenden JC, Trussellllll RR, Hand DW, Howe KJ, Tchobanoglous G (2012) Reverse osmosis. MWHs Water Treatment 17:1335–1414

Custódio E, Llamas M (1996) Hidrología subterrânea. Tomo I y II. Omega, Barcelona

Dawson PA, Elliott A, Bowling FG (2015) Sulphate in pregnancy. Nutrients 4 7(3):1594–1606

Delpla I, Jung AV, Baures E, Clement M, Thomas O (2009) Impacts of climate change on surface water quality in relation to drinking water production. Environ Int 35:1225–1233

Deng B, Zhu P, Wang Y, Feng J, Li X, Xu X, Lu H, Xu Q (2008) Determination of free Ca and Ca-containing species in human plasma by capillary electrophoresis. Medline. 2013. http://www.nlm.nih.gov/medlineplus/

Deng CH, Gong JL, Zeng GM, Niu CG, Niu QY, Zhang W, Liu HY (2014) Inactivation performance and mechanism of Escherichia coli in aqueous system exposed to iron oxide loaded graphene nanocomposites. J Hazard Mater 276:66–76

Dissanayaka CB, Chandrajith R (1999) Medical geochemistry of tropical environments. Earth Sci Rev 47(3–4):219–258

Dissanayake CB, Chandrajith R (2006) Inorganic aspects of medical geology. Z. dt. Ges. Geowiss. 157/3, Stuttgart

Dupont C, Campagne A, Constant F (2014) Efficacy and safety of a magnesium sulfate-rich natural mineral water for patients with functional constipation. Clin Gastroenterol Hepatol 12(8):1280–1287

Durlach J, Bara M, Guiet-Bara A (1989) Magnesium level in drinking water: its importance in cardiovascular risk. In: Itokawa Y, Durlach J (eds) Magnesium in health and disease. Libbey J & Co Ltd, London, pp 173–182

EFSA (2005) Opinion of the scientific panel on contaminants in the food chain on a request of the commission related to concentration limits for boron and fluoride in natural mineral waters adopted on 22 June 2005. EFSA J 237:1–8

EFSA (2016) Panel on dietetic products, nutrition and allergies (NDA): calcium and contribution to the normal development of bones: evaluation of a health claim pursuant to article 14 of regulation (EC) no 1924/2006. EFSA J 14(10):4587

Ekmekcioglu C, Strauss-Blasche G, Holzer F, Marktl W (2002) Effect of sulfur baths on antioxidative defense systems, peroxide concentrations and lipid levels in patients with degenerative osteoarthritis. Forsch Komplementarmed Klass Naturheilkd 9:216–220

Elpiner LI (1995) On the influence of the water factor on the health of Russia's population. Water Resour 22(4):418–425

EU (2011) The Drinking Water Directive (DWD), Council Directive 98/83/EC

Faga A, Nicoletti G, Gregotti C, Finotti V, Nitto A, Gioglio L (2012) Effects of thermal water on skin regeneration. Int J Mol Med 29:732–740

Failde RM (2008a) El água: Hidratación y Salud. Tribunatermal 12:20–27

Failde RM (2008b) El agua: Hidratación y Salud. Tribunatermal 12:20–27

Fraioli A, Sério A, Mennuni G, Ceccarelli F, Petraccia L, Fontana M, Grassi M, Valesini G (2010) A study on the efficacy of treatment with mud packs and baths with Sillene mineral water (Chianciano Spa Italy) in patients suffering from knee osteoarthritis. Rheumatol Int 31:1333–1340

Fenwick A (2006) Waterborne infectious diseases—could they be consigned to history? Science 313:1077–1081

Ferrante M, Rosborg I, Kozisek F (2015) Minerals and mineral ratios in the human body. In: Rosborg I (ed) Drinking water, minerals and mineral balance. Springer, Cham, pp 15–23

Genda H (2016) Origin of Earth's Oceans: Na assessment of the total amount, history, and supply of water. Geochem J 50(1):27–42. https://doi.org/10.2343/geocemj.2.0398

Haque R, Mazumder DNG, Samanta S, Ghosh N, Kalman D et al (2003) Arsenic in drinking water and skin lesions: dose-response data from West Bengal, India. Epidemiology 14:174–182

Health Canada (1997) Water. Ottawa: Ministry of Public Works and Services Canada, Cat. n° 1449-112/1997E. www.hc-sc.gc.ca/ehd/catalogue/general/97ehd215.htm. Ottawa, ON

Huang A, Seité S, Adar T (2018) The use of balneotherapy in dermatology. Clin Dermatol 36:363–368

Hudson-Edwards KA, Jamieson HE, Lottermoser BG (2011) Mine wastes: past, present, future. Elements 7:375–380

Huntington TG (2006) Evidence for intensification of the global water cycle: review and synthesis. J Hydrol 319:83–95

Ishaq MS, Afsheen Z, Khan A, Khan A (2018) Disinfection methods. https://doi.org/10.5772/intechopen:80999

Islam MM, Iqbal MS, Leemans R, Hofstra (2018) Modeling the impact of future socio-economic and climate change scenarios on river microbial water quality. Int J Hyg Environ Health 221, 283–292

Jiang L, He P, Chen J, Liu Y, Liu D, Qin G, Tan N (2016) Magnesium levels in drinking water and coronary heart disease mortality risk: a meta-analysis. Nutrients 8(1):5

Jin S, Fallgren PH, Morris JM, Chen Q (2007) Removal of bacteria and viruses from waters using layered double hydroxide nanocomposites. Sci Technol Adv Mater 8:67–70

Jin L, Whitehead P, Sarkar S, Sinha R, Futter M, Butterfield D, Caesar J, Crossman J (2015) Assessing the impacts of climate change and socio-economic changes on flow and phosphorous flux in the Ganga river system. Environ Sci Process Impacts 17(6):1098–1110

Jones SA, Walter JH (2007) Diagnosis and treatment of severe metabolic acidosis. Pediatr Child Health 17(7):260–265

Karagülle Z, Dönmez A (2002) Balneotherapy for fibromyalgia at the Dead Sea. Rheumatol Int 21:210–211

Karagülle MZ, Karagülle M (2019) Effects of drinking natural hydrogen sulfide (H2S) waters: a systematic review of in vivo animal studies. Int J Biometeorol. https://doi.org/10.1007/s00484-019-01829-4

Karagülle MZ, Tütüncü ZN, Aslan O, Basak E, Mutlu A (1996) Effects of thermal sulphur bath cure on adjuvant arthritic rats. Phys Rehab Kur Med 6:53–57

Kasting JF (1993) Earth's early atmosphere. Science 259(5097):920–926

Kousa A, Havulinna AS, Moltchanova E, Taskinen O, Nikkarinen M, Erikson J, Karvonen M (2006) Calcium: magnesium ratio in local groundwater and incidence of acute myocardial infarction among males in rural Finland. Environ Health Perspect 114(5):730–734

Koziesk F (2003) Health significance of drinking water calcium and magnesium. National Institute of Public Health

Kozisek F, Rosborg I, Selinus O, Ferrante M, Jovanovic D (2015) Background. In: Rosborg I (ed) Chapert 1 of the book Drinking water minerals and mineral balance: importance, health significance, safety precautions. Springer International Publishing, Cham, pp 1–23

Krieger RA (1963) The chemistry of saline waters. Groundwater 1(4):7–12

Leibetseder V, Strauss-Blasche G, Holzer F, Marktl W, Ekmekcioglu C (2004) Improving homocysteine levels through balneotherapy: effects of sulphur baths. Clin Chim Acta 343:105–111

Llamas R (2015) La escasez de água ho yes un mito. Redagrícola, Agosto 2015, 60–62

Marier JR (1968) Fluoride research. Science 159(3822):1494–1495. https://doi.org/10.1126/science.159.3822.1494

Marier JR (1978) Cardio-protective contribution of hard waters to magnesium intake. Rev Can Biol 37(2):115–125

Mennuni G, Petraccia L, Fontana M, Nocchi S, Stortini E, Romoli M, Esposito E, Priori F, Grassi M, Geraci A, Serio A, Fraioli A (2014) The therapeutic activity of sulphate-bicarbonate-calcium-magnesiac mineral water in the functional disorders of the biliary tract. Clin Ter 165(5):e346–e352

Meunier PJ, Jenvrin C, Munoz F, de la Gueronniere V, Garnero P, Menz M (2005) Consumption of a high calcium mineral water lowers biochemical indices of bone remodeling in postmenopausal women with low calcium intake. Osteoporos Int 16(10):1203–1209

Meyrs SS, Patz JA (2009) Emerging threats to human health from global environmental change. Annu Rev Environ Resour 34:223–252

Nassar RA, Browne EP, Chen J, Klibanov AM (2012) Removing human immunodeficiency virus (HIV) from human blood using immobilized heparin. Biotechnol Lett 34:853–856

Neri LC, Hewitt D, Schreiber GB, Anderson TW, Mandel JS, Zdrojewski A (1975) Health aspects of hard and soft waters. J Am Water Works Assoc 67:403–409

Neri LC, Johansen HL, Talbot FDF (1977) The chemical content of Canadian drinking water related to cardiovascular health. Department of Epidemiology, University of Ottawa, Canada

Nicolleti G, Saler M, Pellegatta T, Tresoldi MM, Bonfanti V, Malovini A, Faga A, Riva F (2017) Ex-vivo regenerative effects of a spring water. Biomed Rep. https://doi.org/10.3892/br.2017.1002

Nieuwenhuijsen MJ, Grellier J, Smith R, Iszatt N, Bennett J, Best N, Toledano M (2009) The epidemiology and possible mechanisms of disinfection by-products in drinking water. Philos Trans R Soc 367:4043–4067

Nordstrom DK (2011) Mine waters: acidic to circumneutral. Elements 7:393–398

NSFA (2013). http://www.slv.se/sv/grupp1/Mat-och-naring/Svenska-narings-rekommendationer/Rekommenderat-intag-av-vitaminer-och-mineraler/

Oki T, Kanae S (2006) Global hydrological cycles and world water resources. Science 313:1068–1072

Ortiz AG, Romano RJ, Aretio MB, Moreno AC (1990) Study of the relationship between certain physico-chemical components in the drinking water, hypertension and death for persons with cardiovascular disease [in Spanish]. Rev San Hig Púb 64:377–385

Peacock M (2010) Ca metabolism in health and disease. Clin J Am Soc Nephrol 5:23–30

Pellegatta T, Saler M, Bonfanti V, Nicoletti G, Faga A (2016) Novel perspectives on the role of the human microbiota in regenerative medicine and surgery. Biomed Rep 5:519–524

Pérez-Granados AM, Navas-Carretero S, Schoppen S, Vaquero MP (2010) Reduction in cardiovascular risk by Na-bicarbonated mineral water in moderately hypercholesterolemic young adults. J Nutr Biochem 21(10):948–953

Petraccia L, Liberati G, Masciullo SG, Grassi M, Fraioli A (2006) Water, mineral waters and health. Clin Nutr 25(3):377–385

Pichel N, Vivar M, Fuentes M (2019) The problem of drinking water access: a review of disinfection technologies with an emphasis on solar treatment methods. Chemosphere 218:1014–1030

Pinto B, Reali D (2009) Screening of estrogen-like activity of mineral water stored in PET bottles. Int J Hyg Environ Health 212(2):228–232

Plumlee GS, Morman SA (2011) Mine wastes and human health. Elements 7:399–404

Polya D, Charlet L (2009) Rising arsenic risk? Nat Geosci 2:383–384

Quattrini S, Pampaloni B, Brandi ML (2016) Natural mineral waters: chemical characteristics and health effects. Clin Cases Miner Bone Metab 13(3):173–180

Razowska-Jaworek L (2014) Calcium and magnesium in ground water: occurrence and significance for human health. CRC Press, Boca Raton

Ritter L, Solomon K, Sibley G, Hall K, Keen P, Mattu G, Linton B (2002) Sources, pathways, and relative risks of contaminants in surface water and groundwater: A perspective prepared for the Walkerton Inquiry. J Toxicol Environ Health Part A 65:1–142, Taylor & Francis

Rizzo R, Elia V, Napoli E (2011) The new frontiers of hydrology. IDB 40:232–239

Rosborg I (ed) (2015) Drinking water, minerals and mineral balance: importance, health significance, safety precautions. Springer International Publishing, Cham, 140pp

Rosborg I, Kozisek F (2015a) Macrominerals at optimum concentrations: protective against diseases. In: Rosborg I (ed) Chapter 3 of the book Drinking water minerals and mineral balance:

importance, health significance, safety precautions. Springer International Publishing, Cham, pp 33–52

Rosborg I, Kozisek F (2015b) Macrominerals at optimum concentrations: protective against diseases. Chapter 3 of the book “drinking water minerals and mineral balance: importance, health significance, Safety precautions”, 33-52, Rosborg I (editor), springer international publishing Switzerland

Rosborg I, Gerhardsson L, Nihlgård B (2003) Inorganic constituents of well water in one acid and in one alkaline area of southern Sweden. Water Air Soil Pollut 142:261–277

Rosborg I, Nihlgard B, Gerhardsson L, Sverdrup (2006) Concentrations of inorganic elements in 20 municipal waters in Sweden before and after treatment - links to human health. Environ. Geoch Health 28, 215–229

Rosborg I, Ferrante M, Soni V (2015a) Microminerals at optimum concentrations: protection against diseases. In: Rosborg I (ed) Chapter 4 of the book Drinking water minerals and mineral balance: importance, health significance, safety precautions. Springer International Publishing, Cham, pp 53–77

Rosborg I, Soni V, Kozisek F (2015b) Potentially toxic elements in drinking water in alphabetic order. In: Rosborg I (ed) Chapter 5 of the book Drinking water minerals and mineral balance: importance, health significance, Safety precautions. Springer International Publishing, Cham, pp 53–77

Rosenzweig C, Casassa G, Karoly JD, Imeson A, Liu C, Menzel A, Rawlins S, Root LT, Seguin B, Tryjanowski P (2007) Assessment of observed changes and responses in natural and managed systems. In: Parry LM, Canziani FO, Palutikof PJ, van der Linden JP, Hanson EC (eds) Climate change 2007: impacts, adaptation and vulnerability. Contribution of Working Group II to the fourth assessment report of the Intergovernmental Panel on Climate Change. Cambridge University Press, Cambridge, pp 79–131

Roux S, Baudoin C, Boute D, Brazier M, De la Gueronniere V, De Vernejoul MC (2004) Biological effects of drinking-water mineral composition on calcium balance and bone remodeling markers. J Nutr Health Aging 8(5):380–384

Rubenowitz E, Molin I, Axelsson G, Rylander R (2000) Magnesium in drinking water in relation to morbidity and mortality from acute myocardial infarction. Epidemiology 11(4):416–421. https://doi.org/10.1097/00001648-200007000-00009

Sauvant-Rochat MP, Pepin D (2002) Drinking water and cardiovascular disease. Food Chem Toxicol 40(10):1311–1325. https://doi.org/10.1016/S0278-6915(02)00081-9

Schaerström A, Jørgensen SH, Kistemann T, Sivertun A (eds) (2014) Geography and health: a nordic outlook. The Swedish National Defence College, Stockholm

Schoppen S, Perez-Granados AM, Carbajal A, Oubina P, Sanchez-Muniz FJ, Gomez-Gerique JA, Vaquero MP (2004) A sodium-rich carbonated mineral water reduces cardiovascular risk in postmenopausal women. J Nutr 134(5):1058–1063

Schwarzenbach RP, Thomas E, Hofstetter TB, von Gunten U, Wehrli B (2010) Global water pollution and human health. Annu Rev Environ Resour 35:109–136

Teixeira F (2009). Água, Fonte da Vida. In: Comissão de Coordenação e Desenvolvimento da Região Centro (ed) À Beira da Água, pp 109–139. ISBN: 978-972-569-160-1

Trenberth KE, Jones DP, Ambenje P, Bojariu R, Easterling D, Klein Tank A, Parker D, Rahimzadeh F, Renwick AJ, Rusticucci M, Soden B, Zhai P (2007) Observations: surface and atmospheric climate change. In: Solomon S, Qin D, Manning M, Chen Z, Marquis M, Averyt BK, Tignor M, Miller LH (eds) Climate change 2007: the physical science basis. Contribution of Working Group I to the fourth assessment report of the Intergovernmental Panel on Climate Change. Cambridge University Press, Cambridge/New York, pp 235–336

UNESCO (2009) The United Nations world water development report 3: water in a changing world. UNESCO/Berghahn Books, Paris/New York

Villanueva CM, Cantor KP, Grimalt JO, Malats N, Silverman D, Tardon A, Garcia-Closas R, Serra C, Carrato A, Castaño-Vinyals G et al (2007) Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering, and swimming in pools. Am J Epidemiol 165:148–156

Wallach J (2007) Interpretation of diagnostic tests, 8th edn. Lippincott Williams & Wilkins, Philadelphia

Wang W, Huang G, Jimmy CY, Wong PK (2015) Advances in photocatalytic disinfection of bacteria: development of photocatalysts and mechanisms. J Environ Sci 34:232–247

Whitehead PG, Wilby RL, Battarbee RW, Kernan M, Wade AJ (2009) A review of the potential impacts of climate change on surface water quality. Hydrological Sciences-Journal-des Sciences Hydrologiques 5(1):100–123

WHO (2007) World health report 2007 – a safer future: global public health security in the 21st century, Geneva, Switzerland

WHO (2011a) Guidelines for drinking-water quality, 4th edn. WHO, Geneva

WHO (2011b) Drinking-water guidelines (4th edition): chemical fact sheets. Fluoride. WHO, Geneva

WHO/SDE/WSH/03.04/16 (2003) Background document for the development of WHO guidelines for drinking-water quality

WHO/UNICEF (2010) Progress on sanitation and drinking water: 2010 Update

Wu J, Desch SJ, Schaefer L, Elkins-tanton LT, Pahlevan K, Buseck PR (2018) Origin of Earth's water: Chondritic inheritance plus nebular ingassing and storage of hydrogen in the core. JGR Planets:2691–1712. https://doi.org/10.1029/2018JE005698

Wynn E, Krieg MA, Aeschlimann JM, Burckhardt P (2009a) Alkaline mineral water lowers bone resorption even in calcium sufficiency: alkaline mineral water and bone metabolism. Bone 44(1):120–124

Wynn E, Raetz E, Burckhardt P (2009b) The composition of mineral waters sourced from Europe and North America in respect to bone health: composition of mineral water optimal for bone. Br J Nutr 101(8):1195–1199

Xia XH, Wu Q, Mou XL, Lai YJ (2014) Potential impacts of climate change on the water quality of different water bodies. J Environ Inf:1–14

Yang CY, Chiu JF, Chiu HF, Wang TN, Lee CH, Ko YC (1996) Relationship between water hardness and coronary mortality in Taiwan. J Toxicol Environ Health 49(1):1–9. https://doi.org/10.1080/009841096160952

Yuan QB, Guo MT, Yang J (2015) Fate of antibiotic resistant bacteria and genes during wastewater chlorination: implication for antibiotic resistance control. PLoS One 10:e0119403

Zhu C, Schwartz FW (2011) Hydrogeochemical processes and control on water quality and water management. Elements 7:169–117

Chapter 14
Natural Mineral Water Used in Health Resort Medicine

Frederico J. Teixeira and Celso S. F. Gomes

Abstract Besides chemical composition, the water temperature at the emergence site is, as a rule, a requisite for traditional crenotherapy/balneotherapy practice officially recognized in many European countries as a clinically effective complementary approach in the treatment of low-grade inflammation and stress-related pathologies, the absorption of biologically active inorganic and organic substances through the skin playing an effective role, although the mechanisms of action still remain matter of scientific discussion. The history of balneotherapy and of thermalism, i.e. the economic activity addressed to the prevention, therapy, rehabilitation and wellness provided by the use of hot or warm natural mineral water in thermal resorts or health resort medicine spas. This chapter reports the natural requisites of natural mineral water and spring water to be used in health resort medicine, employing the traditional methods and practices of hydrotherapy, crenotherapy and climatotherapy at the balnearies or bathhouses of the so-called health resort spas.

14.1 Hydrotherapy, Crenotherapy and Balneotherapy: Principles, Methods and Functions

14.1.1 Introduction

Schematically, it can be said that "hydrology" is, etymologically, "the study of water", any water, while "crenology" or "medical hydrology" (a name even more often used in Portugal and other Mediterranean countries) is "the study of natural mineral waters". That is why "hydrotherapy" is "the branch of therapy that deals

---

F. J. Teixeira (✉)
Faculty of Medicine, University of Coimbra, Coimbra, Portugal
e-mail: fredjt@uc.pt

C. S. F. Gomes
Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_14

with the use of water (any water) for prophylactic, curative or rehabilitation purposes" and "crenotherapy" is "the branch of therapy that deals with the use of natural mineral water (formerly called 'mineral medicinal water') for prophylactic, curative or rehabilitation purposes".

In "crenotherapy", natural mineral water is used as a medicine, whether this is done by internal use or by external application of water. That is, "crenotherapy" presupposes the therapeutic use of the constituents of natural mineral water, resulting from its physical-chemical composition (including the possible participation of trace elements), for the direct reason of each or some of its elements or for the conditioned balances in terms of pH, conductivity, etc., that is, in short, its biochemical effects, its activity on pathophysiological problems.

"Crenotherapy" or "balneotherapy" (the first name is the most used in France, the latter name is the most used in Germany), naturally practised in the thermal resort spas using natural mineral water or spring water, will add to the previously mentioned actions due to the water specific physicochemical composition, those actions proper of the "hydrotherapy" in the broad sense of the term (because hydrotherapy can be practised with any water, even outside the scope of thermalism): unspecific topical actions, and the consequent systemic reactions, resulting from the mechanical properties and the thermal properties of water – that is, the thermal effect (stimulating or relaxing on multiple organic functions) of baths, showers, etc., plus the mechanical effects (impulse, massage, compression, etc.) that immersion and the movement in the swimming pool can facilitate, that a shower can develop and that an immersion bath with hydromassage, with air bubble or with underwater shower can provide.

14.1.2 The Efficacy of Medical Hydrology

Not considering here the circumstantial factors (psychological, environmental, climatic, etc.) inherent to a stay at a spa, nor any possible dietary corrections or certain risk factors already experienced in some of them, in the techniques of external application with natural mineral water, the therapeutic effect may result from three groups of factors: (a) hydrotherapy basic factors, which encompass the hydromechanical factors and the hydrothermal factors; (b) crenotherapy specific factors, which depend on the physical-chemical properties of the natural mineral water used in a specific thermal resort spa; and (c) non-specific effects of the thermal resort environment, which encompass environment, climate, hygienic-dietetic care, sociability, relaxation/well-being and psychological.

Table 14.1 shows the natural mineral water factors and the corresponding health effects. Only the two first mention categories, hydrotherapy factors and crenotherapy factors, will be below dealt with.

A. *Hydrotherapy Basic Factors*

Table 14.1 Natural mineral water factors and health effects

A. Common effects in hydrotherapy and crenotherapy	
1. Hydrodynamic factors	
Hydrostatics	
Fluctuation (Archimedes' principle)	
Hydrostatic pressure	
Density, viscosity	
Surface tension (cohesion)	Facilitation of movements
	Cardiovascular effects
Hydrodynamics	Facilitation of the return circulation in lower limbs
Moving surface	Hydrodynamic resistance to movement
Moving direction	
Moving velocity	
Turbulence	
Etc.	
2. Hydrothermal factors	
High specific heat	Peripheral vascular effects
High heat capacity	Sedative and analgesic effect
High vaporization heat	Muscle relaxation (control of muscle contraction, muscle fatigue)
High melting heat	
Thermic conductivity	General activation of the mechanisms of organic defence (type "general adaptation syndrome")
B. Specific effects of crenotherapy	
Water mineralization	Specific pharmacological action:
	Direct action on skin and mucous
	Absorption through ingestion, inhalation and dermal
C. Unspecific effects of thermal environment	
	Psychotherapeutic effects
Environment, climate and sociability	Thermal relaxation/thermal wellness
	Hygienic-dietary care

Hydromechanical Factors These factors are subdivided into two categories: hydrostatic factors and hydrodynamic factors.

Hydrostatic factors – buoyancy force ("Archimedes' principle"), hydrostatic pressure, surface tension, cohesion force, viscosity:

According to Archimedes' principle, "the whole body immersed in a fluid suffers, from the part of that fluid, an impelling force from the bottom up that is equal to the weight of the volume of the displaced fluid". This means that an individual immersed in a swimming pool, for example, due to this bottom-up thrust, will weigh much less, and it can be said that, according to the Lecrenier scheme, when dipped up to the neck, he will weigh about 10% of the real body weight. Therefore, an individual weighing 60 kg will weigh about 6 kg. That is why the bodies submerged in water have a tendency to fluctuate, being for this evident the dependence on the density of the water in question, that is, on greater or lesser mineralization. Such a phenomenon has two immediate effects: it facilitates mobility, from walking to limb movement; it creates self-confidence to the patient who immediately collaborates or self-performs all the proposed kinesitherapy.

Decrease of muscle mass and ligament strength, etc. to move the joints it will be compensated by reducing the body weight or of a body segment (which can be greatly increased when, simultaneously, such immersion is carried out in hot water, with the consequent vasodilation, muscle relaxation and analgesic effect). That is, all movements will be done without overload (body weight), and, at the same time, passive movements of relief (by impulse) can be combined with movements of resistance (by movements of descent, of greater resistance). At the same time, it is possible to create the possibility of standing alone doing exercise and self-convincing the patient that it is possible to do what he was unable to do. It is important to prepare the patient to enjoy hydrokinesitherapy. According to Valenzuela and Babaicoa (1984), it is important to restructure the factors that command the voluntary movement: "power, knowledge and will".

Also, it is important to mention the hydrostatic pressure generated around the dipped body, which in turn depends on the specific weight of the water and, above all, on the absolute height of the water level. This can be used to therapeutically improve evident in the venous and lymphatic circulation, particularly in the blood and lymphatic vessels of the extremities, in the compressed structures and in the large organic cavities – the thoracic perimeter can decrease by 2–3 cm and the abdominal by 2.5–6.5 cm – as has been clearly exposed through the Gauer scheme (cit. in Valenzuela and Babaicoa 1994). This scheme can be therapeutically used to improve the venous and lymphatic system of the lower limbs (varicose veins and lymphedema) and even for respiratory hydrokinesitherapy (there is an increase in the speed of inspiration, without interference with expiration), it can increase the general metabolic activity (especially when also in hot baths), and it increases the urinary volume.

Despite these therapeutic possibilities which must be explored although always under close surveillance avoiding extremism, the truth is that it can also represent a contraindication in cardiac or elderly patients, due to the risk of cardiac or cerebral overload – standing and standing of water, there is usually a relatively low chest pressure, with a weak heart and vessels and low intrapleural pressure; with the water up to just above the waist, much of the liquid content of the legs goes up to the infradiaphragmatic region and also to the thoracic areas; with water up to the neck, fluid volumes rise more, with risk of pulmonary oedema, excess of cardiac influx and consequent increase in stroke volume, increased central venous pressure.

Hydrodynamic factors – the use of water resistance according to the surface to be moved, direction, speed of movement, turbulence, etc.

The resistance to the displacement of a body in the water is correlated, as well as the impulse, with its mineralization and consequent density, the cohesion force, the surface tension, the viscosity, etc.; but, on the other hand, it varies with the surface of the body that slides, the direction of movement or angle of attack and the printed speed, turbulence, etc. The greater or lesser the surface to be mobilized, depending on the shape of the body segment to be mobilized (cleaver hand - cubital edge, or open and frontally presented hand-palmar and hand-dorsal), the greater or lesser the resistance will to displacement. On the other hand, when a body moves into the water, it creates a series of turbulences, more pronounced when water viscosity increases, turbulences that can hinder the movement.

Hydrothermal Factors These are related to the high specific heat, the high heat capacity and the considerable thermal conductivity of the water, as well as the high heat value of the vaporization, factors that allow you to store or lose, take or slowly remove heat from the bodies contact with – mainly by driving (direct application), by convection or by adduction (temperature difference).

The hydrothermal effects will depend on the temperature of the water or the vapours, but also on the body extension in contact, the duration of the application and the individual sensitivity, always having to consider, on the one hand, local effects and general effects and, on the other hand, early effects ("defensive") and late effects ("restorers").

Thus, the main beneficial effects and risks of water temperature above 37 °C (the temperature most used in spas) can be summarized on various organs or systems and functions:

- Cardiovascular system – The capillary and arteriolar expansion with decreased vasoconstrictor sympathetic tone decreased peripheral vascular resistance (on the one hand with increased joint and muscle irrigation, and on the other hand with the possibility of arterial hypotension) and increased cardiac repletion (more effective systole); cutaneous venodilation, but with splanchnic venoconstriction. Hence the risks are as follows: exaggerated hypotension, reflex tachycardia (risks in coronary patients) or exaggerated venous dilation (risks in varicose veins).
- Musculoskeletal system – The decrease in vasoconstrictor sympathetic tone and the increase in vagal tone will favour greater muscle and joint irrigation. At the same time, hydrothermal factors will have an immediate muscle relaxing effect (decreasing muscle tone, excitability and fatigue), followed by a toning effect on active contractility. In the end, the increase in muscle/joint irrigation will add an analgesic, antispastic and sedative effect. If such effects can benefit chronic processes (muscular, tendon-capsular or articular), the respective risks cannot be forgotten in the event of exudative situations or in situations in the process of worsening.
- Respiratory system – A high thermality, in the presence of water or water vapour, leads, on the one hand, to "respiratory polypnea", with its respective advantages, but with the respective risks of respiratory alkalosis, malaise, dizziness and lipotomy, and, on the other hand, bronchodilation, increased respiratory secretions

and the stimulation of the respective trophic activities, an effect so sought after in asthma or in patients with chronic obstructive pulmonary disease.

- Metabolic-endocrine system – A hot bath of water or steam will lead to generalized metabolic-endocrine stimulation, where an increase in corticosuprarenal activity, greater peripheral use of glucose and an increase in cholesterol metabolism are visible and demonstrated, with consequent decreases of cholesterol in blood data analysis, and at the same time a slight increase in urinary pH, much facilitating greater solubilization and the urinary elimination of acid metabolites.
- It should be noted that Benczúr (1939) reviewed the investigations of several hydrologists and compared them with what was described by Selye (1936) in a letter addressed to the editor of the journal *Nature* relatively to what he called "general adaptation syndrome", a general reaction to any type of aggression, which came to be called "stress reaction", and Benczúr also found, as a general basis, a hypothalamic-pituitary stimulation with ACTH (adrenocorticotropic hormone) release. That is, in SAG there will always be a neurohormonal reaction, then interfering with the entire metabolic-endocrine system.
- It will be interesting to highlight the parallelism of the results in relation to uric acid metabolism, lipid metabolism (even more lastingly in the case of thermal therapy), immediate release of corticosteroids (17-ketocorticosteroids) and a decrease in the number of eosinophils (may be interference with allergic factors).
- Nervous system – A hot bath of water or steam induces general sedation, with a decrease in the sympathetic tone and an increase in the parasympathetic tone, schematically resulting in analgesia, general sedation and general antispasmodic effect.

Crenotherapy Specific Factors

The crenotherapy specific factors depend upon the physical and chemical characteristics of the individual waters, and, therefore, they are specific of thermal resorts, and they include those resulting from:

- Direct action on the skin and mucous membranes (particularly evident with sulphurous, chlorinate and silicate waters)
- Topical and/or systemic action of the chemical elements ingested orally or by colorectal absorption (with direct action at the gastrointestinal level or after its absorption)
- Absorption by inhalation or by dermal absorption, with consequent:
- Action of general metabolic, enzymatic or corticosuprarenal stimulation (sulphurous, sulphate, chlorinate, bicarbonate)
- Action after cellular or tissue incorporation (in cartilage and synovial fluid, sulphurous and sulphate waters; in the skeletal muscle, sulphurous and sulphate waters, the last type especially when bearing significant calcium and magnesium contents; or in the hematopoietic system, ferruginous water)

14.1.3 Clinical Research in Medical Hydrology

The question currently most asked by the general population, by health authorities and by many of the doctors themselves is undoubtedly the following: Is hydrological therapy really effective? What "scientific evidence" supports this claim?

At a time when in pharmacological therapeutics the "evidence-based medicine" is almost only regarded as "proof", is it logical to demand the same for hydrological therapeutics? That is, can "proof" of efficacy and safety for thermal therapy be obtained only based on the same methods?

1. The so-called test of time is not discussed here – there will probably not be therapeutic practice used for so long, respected for its safety, affirmed by the patients themselves as beneficial, even if empirically and considering all subjectivity, and systematically sought as a complement or after more or less toxic drug treatments and from which no evident benefits have resulted due to chronic diseases, such as some degenerative rheumatisms, respiratory or ENT (ear, nose and throat) diseases and skin diseases, which, of course, do not satisfy the criteria for a rigorous clinical evaluation.
2. The possibility of carrying out some of the studies, mandatory for medicines, is discussed, such as longitudinal, randomized, simply blind or double-blind trials, comparing with placebo, even if open.

2a. *The need for a clear definition of the intended targets*

- What are the affections for which the therapeutic interest of thermal therapy and its need in the general therapeutic panorama can be claimed?
- Clear definition of the intended benefits, in order to expressly propose which are the "endpoints" and their conditions – degree and duration of clinical effects, influence on health costs, influence on absenteeism, etc.
- Definition or clarification on whether the results are obtained only by crenotherapy or by other associated techniques, or even by the entire "thermal environment".

2b. *Conditioning principles*

The study has to be conducted at the spa, as distinguished from clinical trials with drugs that can be conducted at the hospital or outpatient level – the medicine goes to the patient; here, the patient has to go to the spa.

- Double-blind, comparative, controlled studies are practically impossible to perform in the spa, either due to the organoleptic characteristics of the water (the thermal water has a smell, taste, etc. that prevents blind tests) or due to the technical conditions of the thermal establishment.
- Comparative studies, even if open, are very difficult to carry out, as they would imply that a group of spa patients would be treated with natural mineral water and another group with drinking water – situation that patients will hardly accept – or, in the case of the trial is sequentially crossed, a double period of stay

at the spa, which becomes unaffordable, both in economic terms for the study sponsor (Concessionaire!) and in terms of available volunteers to be submitted to the study because over time they would have to stay at the spa.

The studies to be carried out, although they must be filed with the utmost rigor and must be as close as possible to the standards established for clinical trials with medicines, cannot be removed from the reality of the conditions of operation of the spa (however good they work), i.e. they have to follow the "thermal praxis".

Last but not least, the cost of a clinical drug trial is around a few hundred thousand euro. At the outset, a pharmaceutical industry laboratory already has a past and an economic support that allows it to continuously invest in scientific research (even so, most of that research is only carried out by large multinational firms). The thermal resorts (at least the Portuguese ones) do not have the economic support to invest such tens/hundreds of thousands of euro in hydrological research, and there are no "patrons" willing to sponsor such tests!

3. Publications on the Theme

There are thousands of articles published on balneotherapy/crenotherapy/medical hydrology that any bibliographic research can find in Medline, Medical Excerpt, Cochrane, etc., many of them with very relative value, many detrimental, many still imbued with empiricism and others with little scientific robustness. However, there are also many who already obey, at least partially, the general rules of clinical studies and, therefore, with sufficient scientific strength to be accepted. In fact, there are already many "systematic analyses" or "meta-analysis studies".

14.1.4 Other Notes on Balneotherapy

Balneotherapy (BT) for therapeutic purposes has been practised since ancient times by Greeks and Romans, and through the Middle Ages, Renaissance, Modern and Contemporaneous times, naturally first based on empirical evidences and forward from generation to generation and later based on scientific evidences. The term *balneotherapy* is derived from the Latin word *balneum*, meaning *bath*.

Balneotherapy was practised by the ancient Greeks, Babylonians and Mesopotamians. Homer (c. 750–700 B.C.), a Greek poet and writer and author of the epic poems of "The Iliad" and "The Odyssey", and other classical writers report that the Greeks indulged in a variety of social baths as early as 500 B.C. The Romans were responsible for the popularity and spread of "spa therapy" to other regions of the world. Roman soldiers sought hot baths to recover after prolonged battles. The baths were referred to as "aquae" (Munteanu and Munteanu 2019). There were baths for health recover and baths for hygienics.

The first spas alike those used today spas were built in ancient Greece and Roma. They were called "balnea" and "thermae", the mineral water having source in nearby natural hot or warm springs being mainly applied in bathing for therapeutic and wellness purposes. The word *spa* owes its origin to the name of mountain town called *Spa* located near Liège, in south-eastern Belgium, where a ferruginous or iron-rich mineral spring is used since the fourteenth century to cure rheumatic disabilities. The word spa, meaning fountain, became so popular that the name spa became the common designation for health resorts around the world.

There are some thousands of springs worldwide which are used for healing purposes. The books entitled *Healing Springs: The Ultimate Guide to Taking the Waters* and *Sacred Waters* written by Nathaniel Altman, in 2000 and 2002, respectively, report the identification and specific characteristics of many healing springs worldwide, and the first book referred to was really the first book to present medical evidences that mineral springs can prevent and cure diseases.

Japan, a volcanically active country, has thousands of hot springs, locally called *onsens*, scattered throughout all of its major islands. *Onsens* by definition use naturally hot water from geothermally heated springs. The term *onsen* also extends to cover the bathing facilities and traditional inns frequently situated around a hot spring. Traditionally, *onsens* were located outdoors, although many inns have now built indoor bathing facilities as well. When the *onsen* water contains distinctive minerals or chemicals, the onsen establishments typically display what type of water it is: sulphur onsen, sodium chloride onsen, bicarbonate onsen, iron onsen (Nakata 2008; Serbulea and Payyappallimana 2012). Some of the more notable sand baths can be found in Ibusuki, Kagoshima and Beppu.

There has been achieved scientific evidence about the health benefits on skin diseases of Dead Sea water and of natural spring water (e.g. Proksch et al. 2005; Klein et al. 2011; Dawe et al. 2005; Portugal-Cohen et al. 2011; Seite 2013).

Balneotherapy is recognized as a clinically effective complementary approach in the treatment of low-grade inflammation and stress-related pathologies (Fioravanti et al. 2017; Gálvez et al. 2018). According to these authors, the absorption of biologically active inorganic and organic substances through the skin also plays a role in the effectiveness of *balneotherapy*. However, these same authors state that despite its long history and tradition, the scientific value of BT is still a matter of discussion, more research being needed to clarify the mechanisms of action and effects of BT.

As a matter of fact, both in vitro and in vivo studies have established the water-soluble minerals which are able to permeate human skin (Shani et al. 1985; Halevy et al. 2001; Beer et al. 2003) and seem to be the key mechanism responsible for the improvement in some clinical outcomes, in balneotherapy and mud/peloid therapy (Flusser et al. 2002; Kovács and Bender 2002; Balogh et al. 2005; Yurtkuran et al. 2006; Bálint et al. 2007; Odabasi et al. 2008; Sarsan et al. 2012; Tefner et al. 2013; Branco et al. 2016; Varga 2016; Morer et al. 2017; Corvillo et al. 2017; Antonelli and Donnelli 2018).

Very recently, Cheleschi et al. (2020) have revisited the role of the in vitro studies performed in human and animal samples and have summarized the obtained results on the biological effects of mineral water, in particular on the main rheumatic and dermatological conditions, which take any advantage by BT, and of the regulation of the immune response.

So far, thermal spa waters have been characterized and classified by their inorganic composition. Because the effects of thermal waters on human health are not yet completely known and understood, it would be of interest to identify both inorganic and organic compounds that could be responsible for their biological activity. Some thermal waters of Spain and Italy have only tested for the organic compounds, particularly the volatile ones (DiGioia et al. 2006; Gonzales-Barreiro et al. 2009).

Varga (2012a, b) consider that the quality and distribution of organics in thermal waters are not related to the inorganic content and that the quantities of organics rather reflect the temperatures of natural mineral water and spring water. So far, there is no data on the association of organics and therapeutic efficiency. However, biologically active organic compounds, such as hormone-like molecules (oestrogens), humic substances and oil, bitumen or tar derivatives, can have beneficial (or adverse) health effects via different routes of exposure. Recently, the organic fraction in the thermal waters has been demonstrated as highly bioactive, contributing to the medicinal effects of BT (Szabó and Varga 2019).

With regard to volatile organic compounds, they evaporate with the water vapour causing the characteristic odour of spas. During the therapy, patients inhale several compounds indicated by the fingerprints, and this fact may be a considerable factor of healing, together with dermal uptake of volatile and non-volatile organics. Organic chemical analysis (involving GC fingerprinting) may mean the first step to find the balneological "missing link" between health effects and the chemical composition of waters.

Munteanu et al. (2014) produced an interesting review on balneotherapy and healthy ageing enhancing the mechanisms by which various natural health factors can influence the ageing process. Also, the authors enhance the benefits of the extracts of muds and peloids, currently used in the treatment of various rheumatic, endocrine, dermatological or gynaecological diseases, as well as the properties of the liquid phase of the so-called peloid extract obtained from "Techirghiol mud" is a clear hypertonic solution of minerals, organic humic substances, bituminous, carbohydrates, peptones, amino acids and enzymes, with an alkaline pH of 7.6–8, and mineral content closely comparable to that of blood serum. Formulations based on the extracted mud/peloid are mentioned for cellulite, psoriasis, seborrheic and atopic dermatitis, eczema and first-degree burn treatment.

Ziemska et al. (2019) state that in balneotherapy natural medicinal resources, such as natural mineral waters and spring waters, natural gases and peloids, can play an important role in therapeutic procedures of different health systems. The use of thermal water for medicinal treatment is probably as old as mankind. However, its popularity dropped with the development of effective analgesics and other synthetic medicines. Chemical drugs are reported to cause adverse reactions, including life-threatening ones. At present, because there are several chemicals of synthetic origin, there is a need to search for nonpharmacological approaches and explore natural healing sources, which better fit the human body and cause less adverse effects. The authors discuss the natural medicinal resources referred to and some of their therapeutic applications.

The history of balneotherapy and of thermalism, i.e. the economic activity addressed to the prevention, therapy, rehabilitation and wellness provided by the use of hot or warm natural mineral water in thermal resorts or in health resort medicine spas, can be found in articles produced by the following authors: Jackson (1990), Routh et al. (1996), Ghersetich et al. (2001), Nasermoaddeli and Kagamimori (2005), Maraver (2006, 2008), Failde (2008), Maraver and Armijo (2010), Guérin-Beauvois and Martin (2007), González-Soutelo (2007a, b), Mudry (2015), Sammama (2015), Mourelle and Gómez (2015), Boisseuil (2015), Legido et al. (2015), Meijide-Failde et al. (2015), Pérez- Fernández et al. (2019), and Gómez et al. (2019). Besides historical information, some of the authors referred to highlight the combination of classic techniques with innovative techniques that have enabled the spas to adapt themselves to the demands and needs of a new type of customer.

Balneotherapy (BT) has been considered an effective therapy for the relief of pain attributed to musculoskeletal conditions. There are reports, for instance, the one from Gutenbrunner et al. (2010), that bathing with thermal mineral waters from natural springs or from drilled wells at a temperature of at least 28 °C and with a mineral content of at least 1 g/L was superior in the long term over tap water therapy in relieving pain and improving physical condition.

The healing effect of thermal spring water and of thermal natural mineral water from more or less deep boreholes have been reported; however, further scientific studies are still required in order to define and better understand not only both the water properties and the therapeutic benefits but also the skin structure and functions as well as the transdermal delivery of water-soluble molecules into human skin, the largest and heaviest organ of the body (Schrieber and Gareis 2007; McGrath et al. 2010).

The skin functions as an acidic mantle and has a natural microbial flora. The skin barrier also protects and helps the human body to withstand cold, heat, radiation, external pressure and both mechanical and chemical impacts. About the last subject referred to, Steinsland (2012) produced an excellent investigation of the diffusion of hydrophilic molecules into human skin and the potential effects. And about the interaction of mineral salts with the human skin, Polefka et al. (2012a, b) presented a good literature survey.

Patients suffering from psoriasis and atopic dermatitis have been treated with significant benefits in the Blue Lagoon Clinic, in Iceland, for more than 20 years (Grether-Beck et al. 2008). Recently, growing evidence disclosed the potential therapeutic properties of BT in psoriasis and atopic or contact dermatitis (Huang et al. 2018; Péter et al. 2017).

Rheumatic diseases are now considered one of the biggest social problems competing with mental illness. These diseases are economically and socially big problems for every country. They cause premature disability and high health-care costs. When the principal target of a country is the health and welfare of its people, then disease creates an increased economical strain with similar outcomes. Disease causes a decrease in work production and income and an increase in disability and in medical, pharmaceutical and hospital care. Signs of improvement of the disease appear after curative treatment for many cases of disease, such as gout, degenerative joint disease, ankylosing spondylitis, rheumatoid arthritis, back pain and sciatica (Sukenik et al. 1992; Evcik et al. 2007; Flusser et al. 2002; Codish et al. 2005; Altan et al. 2006; Bálint et al. 2007; Cozzi et al. 2007; Fioravanti et al. 2007, 2010, 2014; Odabasi et al. 2008; Bellometti and Fabbri 2010; Fraioli et al. 2011, 2018; Tefner et al. 2012; Güngen et al. 2012; de Vos et al. 2013; Abu-shakra et al. 2014; Santos et al. 2016; Ciani et al. 2017; Giannitti et al. 2017; Ozkuk et al. 2017; Yücesoy et al. 2019; Gálvez et al. 2019; Szabó and Varga 2019; Corvillo et al. 2019; Cheleschi et al. 2020).

In particular, the work of Fraioli et al. (2018) is a very interesting systematic review of the studies published between 2002 and 2017 on spa therapy, mud-pack therapy, balneotherapy and mud-bath therapy in the treatment of knee osteoarthritis in order to investigate the evidence of the efficacy of such treatment on pain, functional limitation, drug use and quality of life. Overall, 35 studies were examined, and the authors concluded that mud-pack therapy, balneotherapy, mud-bath therapy and spa therapy have proved to be effective in the treatment and in the secondary prevention of knee osteoarthritis, by reducing pain, nonsteroidal anti-inflammatory drug consumption and functional limitation and improving the quality of life of affected patients.

Very recently, Maraver et al. (2018a, b) in an interesting paper disclose new scientific information on the mechanisms of action of mineral elements such as S and Cl, of sulphurous and chloride mineral medical waters used in *thermal medicine*.

The beneficial effects of sulphurous waters when used topically are attributed to S under the form of H_2S, a gas that acts as a gas transmitter participating in several physiological functions, particularly both vascular and angiogenetic activities that cause vasodilation and growth of new blood vessels. The reduced forms of S act over the skin as reductor and keratoplastic; on the respiratory system, reduced S has a mucolytic action improving local circulation, anti-inflammatory, eutrophic and cicatrizing, providing benefits on chronic inflammatory disorders (rhinitis, sinusitis, bronchitis, asthma, etc.); on the digestive apparatus, the protective antitoxic action is enhanced; on the locomotor system, reduced S diminishes inflammation and degradation of the articular cartilage (Fioravanti et al. 2011; Burguera et al. 2014; Meijide 2017; Maraver 2017).

Very recently, Karagülle and Karagülle (2019) made an interesting systematic review of in vivo studies involving rats and mice, of the effects of drinking natural hydrogen sulphide (H_2S) waters. The authors prefer the designation "hydrogen sulphide waters" to the designation "sulphur waters". The last designation was originally and naturally attributed to mineral water containing dissolved H_2S gas with an S^{2-} level of at least 1 mg/L (Karagülle and Dönmez 2002). Because it is difficult to determine which form of H_2S (H_2S, HS^- or S^{2-}) is active, the term "hydrogen sulphide" (H_2S) is the preferred one, since it includes all H_2S-bearing waters. The authors state yet that H_2S health resorts include H_2S water balneotherapy, H_2S mud therapy, H_2S drinking/hydropinic therapy, H_2S water inhalation and Politzer therapies and H_2S water irrigations depending upon the experience and empiric indications of the health resort (Gutenbrunner et al., 2010). Because of their cosmetic effects, other usage of H_2S water or mud is in the cosmetic industry where they are used as ingredients of various cosmetic products (Nunes and Tamura 2012).

Karagülle and Karagülle (2019) mention that in the last decade of the twentieth century, the discovery of endogenous H_2S production in human cells and the recognition of its important role as a gaseous transmitter next to nitric oxide (NO) and carbon monoxide (CO) have changed the understanding of H_2S (Abe and Kimura 1996). It is well recognized that endogenous H_2S has a variety of physiological functions with potential health benefits (Wang 2012; Bełtowski 2015; Bhatia 2015). In the last two decades, there have been intensified efforts for experimental, in vitro and in vivo and clinical studies investigating the effects of natural H_2S waters along with exogenous delivery of H_2S compounds (Szabó 2007; Wu et al. 2016).

The review carried out by Karagülle and Karagülle (2019) provides preliminary insights into the "biological truth" about natural H_2S waters and partly elucidates their potential therapeutic role in balneology and health resort medicine. However, it should be kept in mind that the retrieved preclinical data cannot be directly extrapolated to humans. The authors put forward the question: "Can traditional hydropinic therapies or drinking cures with H_2S waters at natural sulphur water spas or natural (even artificial) H_2S water consumption at home exert similar effects in humans?", a question that remains to be clarified by clinical trials.

Hydrogen sulphide (H_2S) waters are applied mostly in the form of baths defined as H_2S or sulphur balneotherapy and indicated most frequently in the management of rheumatic diseases (Karagülle et al. 1996; Ekmekcioglu et al. 2002; Leibetseder et al. 2004) and a lesser extent in dermatological conditions (Costantino et al. 2005; Huang et al. 2018; Carbajo et al. 2018a, b). Other balneological interventions with H_2S-bearing water are as follows: drinking cure or hydropinic therapy (Scheidleder et al. 2000; Benedetti et al. 2007, 2009; Costantino et al. 2012), inhalations (Contoli et al. 2013; Carubbi et al. 2019), irrigations (Ottaviano et al. 2011) and showers and sprays (Gálvez Galve et al. 2012).

Very recently, Di Marco et al. (2019) have checked based on epidemiological studies the efficacy of the sulphurous mineral water from the Caramanico Terme (Pescara, Italy), which is being administrated since 1576, presently to around 15,000 individuals/year. The efficacy was estimated comparing the effects on one group of 370 individuals to a control group of non-treated 287 individuals. The studies showed pathology-relapses. Also, a subgroup of individuals receiving crenotherapy treatments for more than 5 years presented a highly reduced prevalence of a large spectrum of pathologies (cardiovascular, inflammatory, neurological and cancer diseases) with respect to an overlapping population (in terms of age and gender) of untreated individuals. The studies carried out showed short- and long-term beneficial effects of medicinal mineral water administration.

On the other hand, the beneficial effects of chloride waters, rich in Cl^- and Na^+, when used topically are attributed to changes of cellular osmotic pressure stimulating the nervous cutaneous receptors (Carbajo and Maraver 2018). The nature and extent of the reactions are dependent on the chemical constituents that predominate in water and the respective contents.

Several diseases are treated through the administration of natural mineral waters: *metabolism disorders* (obesity, diabetes, gout, rheumatism), *food or digestive tract diseases* (chronic constipation and diarrhoea), *liver diseases* (hyperaemia, cirrhosis), *diseases of the urinary tract* ("stone" of the kidney), *diseases of the circulatory system* (anaemia, blood pressure) and *diseases of the respiratory system* (pharyngitis, rhinopharyngitis, laryngitis, emphysema). The therapeutic indications for diseases of the digestive, respiratory, musculoskeletal, and dermatological forums is conditioned by the physical and chemical characteristics of the water and the prescribed daily dose (number of doses and volumes of the doses), as well as the precautions should be taken, varies with mineralization, chemical composition and water temperature (Cantista 2011).

Climatotherapy or *Clima therapy* can be defined as the temporary or permanent relocation of a patient to a region with a climate more favourable to recovery from or management of a health condition. *Climatotherapy* comprises alternative treatment methods which are based on the healing properties of natural resources, which include heliotherapy (sun exposure), thalassotherapy (bathing in seawater), balneotherapy (immersion in baths and pools of thermal mineral water) and pelotherapy (topical application of sea mud packs).

In Dead Sea and Black Sea coast, there are famous *climatotherapy resorts* recognized worldwide for its efficacy in the treatment of dermatological and non-dermatological diseases. The beneficial effect of Dead Sea climatotherapy (DSC) for dermatological diseases, such as psoriasis and eczema, is well documented in a multitude of publications, such as Hristakieva (2005), Kazandieva et al. (2008), Kopel et al. (2013), Abu-Shakra et al. (2014) and Emmanuel et al. (2020). *Psoriasis* is a chronic disease that affects about 1–3% of the population of western countries.

Radon balneotherapy consists in the intake of radon, a radioactive natural gas, either by inhalation or by transcutaneous absorption of radon dissolved in water. Radon therapy is applied in inflammatory diseases such as asthma, arthritis and psoriasis (Erickson 2007). Low doses of radon can produce biologically beneficial effects (Feinendegen 2005). Several randomized clinical trials have reported significant long-term beneficial symptom-related effects of radon balneotherapy in rheumatic diseases, lasting up to 9 months after treatment (Franke et al. 2000, 2007a, b; Annegret and Thomas 2013).

14.2 Balneotherapy for Musculoskeletal Pain Treatment: Does the Mineral Content of the Water Matter?

This question had been put forward by several researchers: Waring (2004), Morer et al. (2017), Fioravanti et al. (2017), Gáti et al. (2018), Carbajo and Maraver (2018) and Rapolienė et al. (2019).

Herodotus (484 -? BC), a Greek historian born in the Persian Empire in his contributions to medicine, already noticed that natural mineral springs of different nature are attributed to distinct therapeutic assets. He later, based on his knowledge, created a simple scheme to differentiate the therapeutic indications attributed to various mineral waters (Moss 2010).

In spite of the real effective effects of different mineral waters which have been studied by many researchers, no consistent decisions had been outcome.

Waring (2004) from the School of Biosciences of the University of Birmingham, UK, was one of the first researchers to experimentally demonstrate the permeability of the skin to minerals in aqueous solution; he produced a report on the absorption of magnesium and sulphate across the skin, studying magnesium and sulphate concentrations both in blood and urine of 19 persons (university students and staff members) who were submitted to daily water baths with dissolved Epsom salts at the same time for 7 days. Mg, analysed by flame photometry, and sulphate, analysed by anion high pressure liquid chromatography, concentrations both in blood and urine significantly had increased in almost all the subjects. Really the chemical referred to had crossed the skin barrier.

Morer et al. (2017) believe that treatment methods using mineral water compared with similar treatments using non-mineral water (tap water) have more successful and long-lasting changes of positive nature when measuring pain, function, quality of life, clinical parameters and others. The authors made a systematic review on the specific therapeutic role of mineral elements and other chemical compounds of mineral waters and derivate peloids/muds. A total of 1118 patients suffering from rheumatic and other musculoskeletal diseases were studied: 552 with knee osteoarthritis, 47 with hand osteoarthritis, 147 with chronic low back pain, 308 with rheumatoid arthritis and 64 with osteoporosis.

Carbajo and Maraver (2018) produced a very recent review on the mechanisms of action of natural salt waters used as therapeutic agents in rheumatic and skin disorders. For the authors, salt waters are defined as those with a mineral content of at least 1 g/L of dry residue consisting of over 20% meq/L of both chloride and sodium ions (Maraver and Armijo 2010). Also, Carbajo and Maraver (2018) have mentioned the numerous balneology studies and reviews examining the use of salt waters or of peloids matured in such waters (e.g. those relative to the last 3 years; in *France*, Léauté-Labrèze et al. 2001, Chary-Valckenaere et al. 2018; in *Greece*, Spilioti et al. 2017; in *Germany*, Schiener et al. 2007, Brockow et al. 2007a, b; in *Hungary*, Bálint et al. 2007, Bender et al. 2014, Hanzel et al. 2018, Kulisch et al. 2009, Tefner et al. 2012; in *Israel*, Katz et al. 2012, Matz et al. 2003; in *Italy*, Bellometti 2002, 2007, Cozzi et al. 2007, 2000, Fioravanti et al. 2007, 2011, 2017, Guidelli et al. 2012, Bazzichi et al. 2013, Ciprian et al. 2013; in *Japan*, Agishi et al. 2010, Yoshioka et al. 2019; in *Tunisia*, Fazaa et al. 2014; in *Turkey*, Donmez et al. 2005, Ozkurt et al. 2012, Kesiktas et al. 2012, Karagülle and Karagülle 2015, Karagulle et al. 2007, 2017, 2018, Ozkuk et al. 2017, Kardes et al. 2018).

Also, based on the experience of the authors below referred to, the topical use of natural salt waters and their mud/peloid products in both balneotherapy and thalassotherapy has yielded good outcomes essentially in the treatment of rheumatic and skin disorders, specifically in the following treated conditions or disorders: *osteoarthritis* (Elkayam et al. 1991; Bálint et al. 2007; Bellometti et al. 1997a, b, 2007;

Karagulle et al. 2007; Cantarini et al. 2007; Fazaa et al. 2014; Gyarmati et al. 2017; Ozkuk et al. 2017; Hanzel et al. 2018), *rheumatoid arthritis* (Elkayam et al. 1991; Bellometti et al. 2000; Codish et al. 2005; Branco et al. 2016; Santos et al. 2016; Karagulle et al. 2017; Fraioli et al. 2018; Karagulle et al. 2018), *back pain or spondylitis* (Constant et al. 1995; Balogh et al. 2005; Cozzi et al. 2007; Kulisch et al. 2009; Tefner et al. 2012; Kesiktas et al. 2012; Karagulle and Karagulle 2015), *fibromyalgia* (Bellometti and Galzigna 1999; Fioravanti et al. 2007; Guidelli et al. 2012; Ozkurt et al. 2012; Bazzichi et al. 2013; Pérez-Fernández et al. 2019) and *psoriasis* (Halevy and Sukenik 1998; Tsoureli-Nikita et al. 2002; Schiener et al. 2007; Brockow et al. 2007a, b; Péter et al. 2017).

Rapolienė et al. (2019) had studied the effect of mineral water with different mineral contents on musculoskeletal pain and related symptoms experienced. The consumption of pain medication has significantly decreased in all mineral water groups.

14.2.1 The Mechanisms of Action of Balneotherapy Still Are Not Fully Clear

Balneotherapy (BT) is one of the most commonly used complementary therapies for many pathological conditions: dermatological, rheumatological, gastroenterological conditions, pulmonary diseases, cardiovascular, gynaecological, metabolic, neurological, psychiatric and endocrine disorders (Contoli et al. 2013; Fioravanti et al. 2017; Forestier et al. 2016; Guidelli et al. 2012; Katz et al. 2012; Matsumoto 2018; Naumann and Sadaghiani 2014; Tenti et al. 2015; Cheleschi et al. 2020). Balneotherapy beneficial effects are related to physical and chemical factors, but the exact mechanism of action is not fully understood (Cheleschi et al. 2020).

According Fioravanti et al. (2017), despite the increasing number of preclinical and clinical studies, many gaps still remain on the understanding and on achieving full consensus within the scientific community of such mechanisms. One of the critical points is the absorption of the minerals through the skin and their consequent articular concentration, for instance, in the case of OA, a common rheumatic functional disability. In the authors' opinion, more studies are needed about the specific effects of various mineral waters and about the ideal concentration of each element in order to achieve an optimal response. On the authors' great experience, there is so far substantial clinical evidence, based on various systematic reviews and meta-analyses on BT for OA, suggesting that balneotherapy is an effective and well-tolerated complementary therapy for OA, although the results of the existing studies are not strong enough to draw firm conclusions (Espejo-Antúnez et al. 2013; Varga 2016; Forestier et al. 2016).

Varga (2016) considers that the therapeutic activity of the natural resources – thermal spa waters and *peloids* – is mainly linked with the inorganic content of thermal waters and *peloids*. He considers too that experimental balneological studies should be properly designed, contemplating more treated groups, including negative controls, and points out the lack of studies involving their organic content. Clinical studies generally and mainly involve the double-blind method or the meta-analyses or yet systematic reviews (Szucs et al. 1989; Kovács and Bender 2002; Pittler et al. 2006; Falagas et al. 2009). The overall benefit is most probably the result of a complex synergistic combination of several factors: mechanical, thermal and chemical effects (Bender et al. 2002; Failde 2008; Guidelli et al. 2012; Gomes and Silva 2012; Fioravanti et al. 2011, 2017; Torres et al. 2015; Tenti et al. 2015; Cantista 2016).

Very recently Carbajo and Maraver (2018) had proposed a new mechanism of action particularly specific for salt waters employed in health resort medicine, after examining models of cutaneous sorption and desorption, dissolved ion mechanisms of skin permeance (osmosis and cell volume-driven mechanisms in keratinocytes, and the behaviour of salt waters as stimulators of mechanosensitive ion channels). For the authors referred to when topically applied such saline waters or mud/peloid rich in Cl^- and Na^+ would act on the skin either directly or via mud/peloid containing the tose salts by modifying cell osmotic pressure, which in turn would stimulate skin nerve receptors, via piezoelectric ion channels embedded in cell membranes, called “Piezos”.

Carbajo and Maraver’s proposal was based on the previous work by Carbajo et al. (2014) who using non-invasive examination techniques used a mud prepared mixing magnesium bentonite and salt waters from the Cofrentes health resort (in Valencia, Spain).

Bathing in thermal waters rich in minerals, sometimes highly saline waters, can be taken outdoors the health resort medicine facilities, in most cases without medical surveillance.

Figures 14.1, 14.2, 14.3 and 14.4 show some natural sites where bathing is currently carried out outdoors without any professional counselling and supervision.

14.3 Balneotherapy in Portugal

14.3.1 Historical Facts

Since ancient times, man has been using thermal waters to achieve physical and psychological well-being. Until the twelfth century, that is, until the foundation of Portugal, the thermalism went through several periods: pre-Roman, Roman-Lusitanian, post-Roman, Luso-Germanic and Arabic.

The Romans, in Portugal, were the great promoters of the thermalism; they valued the so-called thermal mineral-medicinal waters and developed the practices and methods of hydrotherapy. The balnearies were part of a civilization that seeks to expand through its vast empire a culture in which pleasure, combined with the health of body and mind, was a right of citizenship. In the Lusitania territory, spas did appear in Lisbon, Tróia, Estoi, Conimbriga, Entre-os-Rios, S. Vicente, Vizela,

Fig. 14.1 Blue Lagoon, near Grindavik, Reykjanes Peninsula, Iceland. The average seawater temperature is 39 °C all year round. The warm seawater is rich in minerals such as silica that do wonders to the human skin. Blue Lagoon is man-made, the water being a by-product of the Svartsengi geothermal power station. Silica deposition forms soft white mud on the bottom of the lake which bathers rub on themselves. The superheated water is vented from the ground near a lava flow and used to run the turbines that generate electricity. After going through the turbines, the steam and hot water passes through a heat exchanger to provide heat for a municipal water heating system. Then, the water is fed into the lagoon

Taipas, Chaves, Caldelas, São Pedro do Sul and Gerês, more sumptuous or more modest, but always functional and playful.

The church, once adverse to the practice of public baths, took advantage of the hydromineral therapy by placing the bathhouses under its direct jurisdiction. Convents, abbeys and bishoprics began to explore the baths.

Figure 14.5 shows the so-called Stone Fountain located next to Rainha Dona Amélia balneary, in Várzea, São Pedro do Sul, where sulphurous silicate, fluoride and sodium bicarbonate water with pH = 8.89 (estimated at 18 °C) emerges at 67.8 °C. The water used for balneotherapy is provided from a deep-seated (500 m) artesian borehole. In the spa of São Pedro do Sul, there is another balneary called D. Afonso Henriques. The two bathhouses or balnearies of the São Pedro do Sul spa or health resort are among all Portuguese bathhouses the most frequented.

The use for curative purposes of the Caldas hot springs and Lafonenses thermal natural mineral waters, as they were called until the nineteenth century, the thermal spa of São Pedro do Sul dates back more than 2000 years. During the first years of century I, the Romans built the Roman Balneum in the so-called Bath Village, which remained in ruins for many years. Fortunately, in 2018, recovery work began.

Fig. 14.2 Ponta da Ferraria, Ginetes, São Miguel Island, the Azores archipelago: natural piscines of thermal sulphurous seawater. The water is warmed by a geothermal spring existing beneath, and its temperature is around 30 °C at the peak of the low tide and around 18 °C at the peak of the high tide

Fig. 14.3 Natural piscine of thermal waters of Caldeira Velha, São Miguel Island, the Azores archipelago, where bathing is a current practice. The water source of the thermal pool is a waterfall of warm, iron-rich mineral water. Caldeira Velha is located on the north slope of the Fogo Volcano

Fig. 14.4 Thermal pools of Pamukkale in Denizli, south-western Turkey, used for thermal baths. In this World Heritage Site, there are several hot Ca- and CO_2-rich springs, which water temperature ranges from 35 °C to near 100 °C. The terrace's walls are made of travertine, a variety of limestone precipitated from water degassing

The thermal complexes built by the Romans comprised two spaces for different uses: a medicinal bath ("balneario"), another of hygienic and recreational type (thermae), both with separate spaces for men and women. Thermae, the rooms adjacent to the spa, were the Romans' favourite leisure places for bathing, massage, conversation and physical exercise, that is, to achieve the well-being of the body and the spirit. The temperature of the water in the bathrooms was gradual: cold, *frigidarium*; temperate, *tepidarium*; hot, *caldarium*; very hot, next to the oven, *praefurnium*.

With the Islamic occupation, there was continuity of the use of the Termas or Roman Caldas. The baths with thermal and mineral-medicinal waters were called *hamma* (the Castilian term for Alhama), and baths with hygienic function taken in different rooms in the temperature graduation were called al-Hammam.

In 1152, the first king of Portugal, Dom Afonso Henriques (1109–1185), granted the first Foral to Vila do Banho, and in 1169, having fractured one leg in the battle of Badajoz against the Arabs supported by the kingdom of Leon, was physically recovering in Caldas Lafonenses, then called Vila do Banho. The development of Caldas Lafonenses eventually gave rise to the "Hospital Real das Caldas de Lafões" created by Rei Dom Manuel I or King Manuel I (1469–1521).

Fig. 14.5 Source of the Stone Fountain in Várzea, São Pedro do Sul, where sulphurous mineral-medicinal thermal water emerges at 67.8 °C and is only used in external applications in the treatment of diseases of the respiratory tract, muscles, joints and skeleton, and also of the skin

In 1884, the S. Pedro do Sul Town Council built a modern spa to replace the almost 300-year-old "Hospital Real das Caldas de Lafões". In 1984, Rainha Dona Amélia de Orleães or Queen Amelie of Orleans (1865–1951) did successful treatments in the modern spa, and in 1985, a Royal Decree determined the change of the name of "Hospital Real das Caldas de Lafões" to "Balneário da Rainha Dona Amélia". And, under the Republican system initiated in 1910, the thermal health resort was rechristened to "Termas de São Pedro do Sul".

In 1987, the new thermal health resort named "Balneário Dom Afonso Henriques" was inaugurated, and modernization works were initiated in the existing spa "Balneário Rainha Dona Amélia". Presently the thermal water used in both bathhouses has the source in a deep-seated borehole, AC1, 500 m deep, and crossing Hercynian granite emerge at 67 °C. This water classified as sulphurous and sodium bicarbonate could replace the traditional spring characterized by much smaller output.

In Portugal, there are other thermal health resorts built and utilized by Romans in first, second and third centuries A.C., such as Caldas de Chaves (the name Aquae Flaviae was given to the town by the Emperor Titus Flavius Vespasianus) and Caldas das Taipas. According to Carneiro (2015), in the town of Chaves, the Roman spa complex was built directly atop the hot mineral springs (76 °C). Two main building phases were identified: phase I dated of the first century A.C and phase II corresponding to a major renewal of the complex ascribed to the late second or early third centuries A.C. The archaeological Roman Aquae Flaviae site was just discovered in 2006 during the construction of an underground car park right in the centre of the town of Chaves, and it is considered the largest and best preserved Roman thermal spa so far known in the Iberian Peninsula. The exploration of Caldas de Chaves was licensed in 1899, but only about 50 years later the actual existing spa complex and "buvette" was built enabling the use in good conditions of the sodium bicarbonate, gasocarbonic and mesosaline natural mineral water characterized by pH = 6.8 and a total mineralization of 2625 mg/L to heal digestive, respiratory and muscular-skeletal pathologies.

The use of natural mineral water in the baths or balnearies, not only for hygienic reasons but also for health reasons, goes back to the Egyptian and Greek peoples, but were the Romans who pushed the construction of the structures of the so-called public baths and the so-called aqueducts for water transportation and water supply.

The empirical and scientific knowledge is long and vast relatively to the benefits of mineral water to human health, whether ingested or in the form of baths. In Portugal, there is the oldest thermal hospital in the world, the Caldas da Rainha Thermal Hospital, founded in 1485 by Rainha Leonor de Lencastre or Queen Eleanor of Lancaster (1458–1473), currently closed and awaiting a recover intervention. It was due to the Portuguese physician Francisco da Fonseca Henriques, who was a medical doctor of the Royal House contracted by the king D. João V, the first known inventory of Portuguese hydrological resources, containing references to several Termas or Caldas and their medicinal potentialities. All the available information was collected in the book entitled *Aquilégio Medicinal*, edited in 1726 that can be considered a Therapeutic Hydrology Treaty. From then on, the Caldas began to be frequented by the elites as centres of leisure and recuperation, and, with periods of greater or lesser interest and also by the common citizen, the thermalism has remained active until the present time. It was vulgar to say "Go to Waters" or "Go to Baths". In Portugal, it was at the turn of the nineteenth to the twentieth century that the so-called golden age of thermalism began, booming in the 1950s and 1960s of the twentieth century.

In recent times became evident the crisis that plagues the Portuguese thermalism, so much so that in order to increase the attraction of people by the spa, through Decree-Law 142 of July 11, 2004, the thermal activity is no longer confined to treatment of diseases by the water and to allow the application and benefit in the thermal resorts of programmes of leisure, relaxation, beauty and aesthetics. In Portugal, in recent years, there had been a remarkable rejuvenation and re-qualification in the baths or balnearies and in the complementary infrastructures of the thermal health resorts. More than 300 million euro had been invested in the programmes.

In addition to the traditional thermal offer aimed at the treatment of pathologies of the respiratory, musculoskeletal, rheumatic and digestive forums, *thermal wellness* was contemplated too related to the prevention of disease, through the promotion of healthy lifestyles, contemplating, for example, relaxation activities including pedestrian, equestrian and cycling tours, fitness in the gym or open air, massage programmes (including Vichy shower), diet programmes and cosmetic and beauty treatments in spa environment.

Since 2010, the thermal health resorts have registered a decreasing number of aquists, when the Portuguese State stopped to share financially the thermal treatments due to the economic crisis that began in 2008. However, the recovery to the times of pre-crisis is being gradual, and in 2016 there was a growth of about 50%

compared to 2015. In 2016, the thermal business including therapeutic and wellness treatments was valued at 14 million euro (Barbosa 2017).

Among the European countries with a thermal tradition, Germany, France, Spain, Greece, Iceland, Hungary and Czech Republic, the thermal treatments are subsidized by the national health systems or by the insurance companies.

Hopefully, in 2019, the Portuguese SNS (Serviço Nacional de Saúde, i.e. the National Health Service) is subsidizing (about one-third of the cost of all the treatments medically recommended) the thermal treatments, in case they are medically prescribed. However, it is true that it is said that what is spared in a way is spent in another way on more medications and more frequent care in the health services. At the moment, there is much talk of health tourism in which the thermal therapeutic offer must be integrated.

In Portugal, the health tourism aims at enhancing national revenue taking advantage of specialized medical resources, logistics equipment, the diversity and uniqueness of the natural environment and climate amenity, assets that will enable to attract people from all over the world to benefice from specialized and innovative surgeries and specialized medical treatments of short duration, and also from programmes of recovery of traumatic effects and anti-stress programmes.

The main attraction point of any thermal resort should be the spa and also the adequacy and technical and scientific innovation of the methodologies that are practised in order to promote the best therapeutic benefits of the specific properties of its natural mineral water, which naturally need to be thoroughly studied and characterized.

The prescription of treatments with *natural mineral water* reckoned by their medicinal properties, like any medicine, is the responsibility of specialized medical doctors. Medical hydrology is a medical specialty recognized since 1995 by the WHO (World Health Organization). The so-called medical mineral water is a natural mineral water possessing recognized and interesting therapeutic properties or simply that it provides health benefits through the action of its nature and mineral content (trace elements or other bio-essential chemical elements) and can be used more for external applications but, in some cases, also for internal oral applications).

In Portugal, as mentioned above, there are 41 active thermal baths, which are more represented in the northern and central regions of the country. In the 41 active health resort medicine establishments existing in the country, the search for health resort medicine and wellness already represents 60% of the spa business versus 40% of the classic thermalism (Azevedo and Vasconcelos 1995; ATP 2009).

In recent years, some thermal resorts, due to research and development carried out in universities and laboratories, have found in the cosmetics and the production of dermotherapeutic products a new business sector taking advantage of the characteristics of their specific thermal waters. Creams, lotions (body, face cream, facial tonic, cleansing milk) and soaps are some of the products marketed. Caldas da Felgueira, S. Pedro do Sul, Caldas de Chaves and Caldas das Taipas are examples of thermal resorts where this new activity is happening.

The development of specific therapeutic and cosmetic peloids with own brands of the thermal health resorts is still lacking. Peloids in which the main active ingredient is the thermal water of a certain thermal spa and other differentiating products with certain functionalities can be developed: anti-infection, anti-allergic, anti-inflammatory, anti-psoriasis, anti-acne, anti-seborrhoea, function of the incorporation in the pastes of suitable functional additives essentially of pharmaceutical grade. Research for these purposes is being developed at the GeoBioTec Research Unit in the University of Aveiro.

14.3.2 Current Situation

In recent times, there has been evidence of the crisis that plagues the Portuguese thermalism, so much so that in order to increase the attraction of people by the health resort, through Decree-Law 142 of July 11, 2004, the thermal activity is no longer confined to treatment of diseases by the water and to allow the application and benefit in the thermal resorts of programmes of leisure, relaxation, beauty and aesthetics.

Hydrotherapy seeks not only the therapeutic effects of water arising from the chemical composition of water but also the effects of the thermal and mechanical properties of water. At present, the term *hydrotherapy* has limited meaning to the benefit of the thermal and mechanical properties of the water of the net, as it happens in the water gymnastics and the “Jacuzzi”.

In turn, the term *crenotherapy* is applied to a set of practices that take into account the therapeutic benefits of mineral-medicinal water, when it is ingested in a controlled way, when it is applied topically or even when it participates in the composition of peloids used in hair therapy.

The so-called *hydropinic* treatments or treatments by ingestion of mineral water consist of the medically controlled intake of certain types of mineral-medicinal water. However, only certain mineral-medicinal waters may be ingested for therapeutic purposes which are conditioned by the respective chemical compositions.

The natural mineral-medicinal water of São Pedro do Sul Thermal Resort, given its relatively high content in reduced forms of sulphur HS^- and S_2^-, is a good example of water that should not be ingested. The hydrogen sulphide present in the deep-seated well water or borehole could most probably arise, either from hydrolysis of sulphide minerals present in the rock reservoir or from the action of sulphate--reducing bacteria.

Hydrogen sulphide gas causes the “rotten-egg” or sulphur water smell. Hydrogen sulphide is a broad-spectrum poison, meaning that it can poison several different systems in the body, although the nervous system is most affected. The toxicity of H_2S is comparable with that of carbon monoxide, it binds with iron in the mitochondrial cytochrome enzymes, thus preventing cellular respiration. Hydrogen sulphide is created by the human body in small doses through bacterial breakdown of proteins containing sulphur in the intestinal tract; it is also produced in the mouth (halitosis).

The WHO issued a background document entitled “Hydrogen Sulfide in Drinking-water” for the development of WHO Guidelines for Drinking-water Quality (WHO/SDE/WSH/03.04/07, only in English).

WHO Guidelines for drinking-water quality (GDWQ) were published in three volumes: Volume 1 – Recommendations; Volume 2 – Health Criteria and Other Supporting Information, issued in 1996; and Volume 3 – Surveillance and Control of Community Supplies. The second editions of these volumes were published in 1993, 1996 and 1997, respectively, and addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. However, hydrogen sulphide in water causes no known health effects. High concentrations of H_2S do change the taste of the water. No data are available on the oral toxicity of hydrogen sulphide. However, there are evidences that alkali sulphides irritate mucous membranes and can cause nausea, vomiting and epigastric pain following ingestion. Spring waters that contain elevated concentrations of hydrogen sulphide are used for therapeutic medicinal baths (Calado 1988, 2001; Bos et al. 2015; Carbajo and Maraver 2017; Carbajo et al. 2018).

According to the WHO, the taste and odour threshold for hydrogen sulphide in water has been estimated to be as low as 0.05 mg/litre. However, hydrogen sulphide should not be detectable in drinking water by taste or odour. Although oral toxicity data are lacking, it is unlikely that anyone could consume a harmful dose of hydrogen sulphide in drinking water. Consequently, no health-based guideline value is proposed.

Karagülle and Karagülle (2019) made a systematic review aimed to evaluate in vivo experimental studies investigating the biological effects of natural H_2S water drinking in healthy or with disease model laboratory animals. However, it should be kept in mind that the retrieved preclinical data cannot be directly extrapolated to humans. Additionally, most of the included studies were rated for unclear risk of bias across all categories except random allocation, reflecting very poor reporting of methodological details. These limitations should be addressed when planning similar studies in the future. The question “can traditional hydropinic therapies or drinking cures with H_2S waters at natural sulphur water spas/health resorts or natural (even artificial) H_2S water consumption at home exert similar effects in humans?” remains to be clarified by clinical trials. Also, it is due to these reduced forms of sulphur that the mineral-medicinal water of Portuguese sulphurous waters ought their curative power to diseases of the respiratory, musculoskeletal and dermatological systems.

The antimicrobial and keratolytic effects of sulphur (S) are well known, and the importance of sulphur in dermatology and cosmetology is well recognized, and sulphur is known to be an important component of the skin. One hundred grams (100 g) of fresh skin contains 0.80–2.50 g of sulphur, which intervenes in the composition of the molecules cristine, cisteíne and glutathione molecules. As in minerals there are no two natural mineral waters alike; each water has a genetic signature or DNA, depending on its hydrobiochemical composition.

Today, the chemical, physical or physicochemical properties of natural mineral waters are relatively well known, as is not the case with a microbiological component, also called *microbiota* or *microbiome*. In the microbiological component, only the pathogenic microorganisms (due to the negative impacts they have on human health) have been studied. The other microorganisms and their metabolites can be factors justifying the therapeutic properties of mineral-medicinal waters (Morais and Costa 2012; Gómez and López 2015; Meijide-Faílde et al. 2015).

The *microbiota* of a natural mineral water is the bacterial, pathogenic and non-pathogenic flora, which is very constant, which contains, at the outlet of the spring, flora whose qualitative and quantitative composition must be controlled through periodic analyses (Directive 2009/54/EC).

The use of *natural mineral water*, associated natural resources and thermal tourism are important contributions to the economy of the region where it occurs. As has been said, *spring water* is a water of underground circulation and bacteriologically appropriate in its natural state for human consumption.

Portugal is a country rich in natural mineral water of varied chemistry (bicarbonate, chloride, sulphate, sulphurous, fluoride, and silicate) that has been used for medicinal purposes for many years in establishments called Termas.

The first publications on Portuguese “Mineral Waters and Thermal Resorts” were as follows: *Banhos de Caldas e Águas Minerais* by Ramalho Ortigão (first edition dated 1875 and last edition dated 1944), *Le Portugal Hydromineral* by Luiz Correa Acciaiuoli (Acciaiuoli 1952) and *Hidrologia Médica: Águas Minerais de Portugal* by Feliciano Guimarães and Lobato Guimarães (Guimarães, Guimarães 1954).

Natural mineral water is defined as a bacteriologically acceptable mineral water of deep or extensive circulation in the Earth’s crust, which has stable physical and chemical properties at its origin and can provide interesting therapeutic properties or simple health-friendly effects, due to its nature and mineral content (trace elements or other constituents). Each *natural mineral water* has a genetic signature or DNA, depending on its hydrobiochemochemical composition.

The chemical classification of natural mineral waters depends on the dominant anion or cation: bicarbonate water, sulphate water, chloride water, calcium water, magnesian water, sodium water, etc. when the ion which gives it its name is equal to or greater than 20% of the anionic or cationic composition total, expressed in milliequivalents. Other anions or less common cations and even dissolved gases can occur in natural mineral waters equally of medicinal interest and their contents allowing the classification of these waters.

According to Teixeira (2017), water mineralization (estimated by the mass of the dry residue (DR) measured after heating at 180 °C) is used to classify natural mineral waters as follows:

1. *Very poorly mineralized water* – total mineralization equal to or less than 50 mgL^{-1}

2. *Slightly mineralized water* – total mineralization equal to or less than 500 mgL^{-1}
3. *Meso- or mediomineralized water* – total mineralization between 500 and 1500 mgL^{-1}
4. *Strongly mineralized water* – total mineralization equal to or greater than 1500 mgL^{-1}

In the case of gasocarbonic waters, the dry residue (DR) value is less than total mineralization value, due to gaseous evolution of CO_2 and consequent mass loss, during the analytical determination.

And as for anions the European Union established the following types of natural mineral water:

1. *Iron-rich or ferruginous water* – containing 5 mgL^{-1} or more of total iron
2. *Sulphurous water* – containing 1 mgL^{-1} or more of sulphur in the form of H_2S and reduced forms HS^- and S^{2-}
3. *Carbonate gas water* – containing 250 mgL^{-1} or more free CO_2
4. *Bicarbonate water* – containing bicarbonate content (HCO_3^-) higher than 600 mgL^{-1}
5. *Sulphate water* – containing sulphate content (SO_4^{2-}) exceeding 200 mgL^{-1}
6. *Chloride water* – chloride content (Cl^-) higher than 200 mgL^{-1}
7. *Fluoride water* – fluoride (F^-) content higher than 1 mgL^{-1}

As for cations the natural mineral waters are classified as:

1. Sodium when the sodium content (Na^+) is higher than 200 mgL^{-1}
2. Calcium when the calcium content (Ca^{2+}) is higher than 150 mgL^{-1}
3. Magnesium when the magnesium content (Mg^{2+}) is higher than 50 mgL^{-1}

Maraver and Armijo (2010) and (Maraver et al. 2018a, b) for mineral medical waters used in Spanish balnearies had defined chloride waters as those that have TSD (total solids dissolved) > 1 g/L and $\geq 20\%$ meq/L of ion chloride (Cl^-); the same authors had defined sulphurous waters as those that have reduced sulphur ($HS^- + H_2S$) ≥ 1 mg/L.

The "Escuela Profesional de Hidrologia Médica" of the Facultad de Medicina de la Universidad Complutense de Madrid, Madrid, Spain, has adopted for mineral medical waters classification a criterium based on ionic composition expressed in equivalents of the predominating constituents (see Table 14.2).

Natural mineral waters are also classified by other physical parameters, such as pH, temperature, hardness, chemical parameters, molecular concentration/osmotic pressure and radioactivity.

With regard to pH, natural mineral waters are classified as *acid waters* (pH 7.0) and *neutral waters* (pH = 7.0).

Still regarding pH, Carvalho (1955) has classified the Portuguese natural mineral waters in five groups: alkaline, pH ≥ 7.5; neutral, $7.5 < \text{pH} \geq 6.75$; weakly acid, $6.75 < \text{pH} \geq 6.0$; acid, <6.0 pH ≥ 4.4; and very acid, pH ≤ 4.4.

In Portugal, as a rule, the pH of *natural mineral water* is within the range of 5.5–8.5. Practically almost all sulphurous natural mineral waters which are

Table 14.2 Classification of natural mineral medical waters

Predominating ion	Criteria	Classification
Chloride, Cl^-	≥ 20% meq	Chloride
Sulphate, SO_4^{2-}	≥ 20% meq	Sulphate
Bicarbonate, HCO_3^-	≥ 20% meq	Bicarbonate
Sodium, Na^+	≥ 20% meq	Sodic
Calcium, Ca^{2+}	≥ 20% meq	Calcic
Magnesium, Mg^{2+}	≥ 20% meq	Magnesic
Iron, Fe^{+2}	≥ 5 mg/L	Ferruginous
Sulphur (reduced), $HS^- + H_2S$	≥ 1 mg/L	Sulphurous
Carbonic gas, CO_2	≥ 250 mg/L	Gasocarbonic
Radon, Rn	≥ 67.3 Bq/L	Radioactive

prevalent in northern and central regions of the country, most used for health resort medicine, are alkaline, pH = 8–9.4, and only two natural mineral waters have higher pH values, Caldas de Monchique with pH = 9.5 and Caldas de Cabeço de Vide, a rare sulphurous water, with pH = 11.5. In São Miguel Island, the Azores archipelago, there are natural mineral waters of volcanic origin, in Ribeira Grande and in Furnas, which show extremely acid pH, 0.3–3.0.

With regard to natural mineral water temperature, according to Teixeira (2017), natural mineral waters are classified into two main groups based on the temperature measured at its emergence site: *cold waters*, emerging at temperature 25 °C.

And hot waters are subdivided into three subgroups:

1. *Hypothermal* – if they emerge at temperatures between 25 and 35 °C, such as the waters of the Monfortinho and Unhais da Serra Termas, in the central region of Portugal
2. *Mesothermal* – if they emerge at temperatures between 35 and 50 °C, such as the waters of the Felgueira and Manteigas Termas, in the central region of Portugal
3. *Hyperthermal* – if they emerge at temperatures above 50 °C, such as the waters of Chaves and São Pedro do Sul Termas

This classification has been adopted by the Hydrology Institutes of Coimbra and Porto (Guimarães and Guimarães 1954; Teixeira 2017). Nevertheless, controversy persists in Europe about the classification of natural mineral water in terms of temperature, particularly when the water is used in health thermal resorts, since the natural mineral waters used in thermal balnearies are called *thermal waters*, just because they are used in the aforesaid health thermal resorts. In Germany and in other European countries, thermal waters are only those that emerge at temperatures above 20 °C.

The Portuguese designation "Termas" or "thermal balnearies" does not imply the existence of hot or thermal waters. The thermal waters are natural mineral waters whose temperatures measured at the emergence point exceed the average air temperatures measured at these same places by 4 °C. In turn, the "Termas" or "thermal balnearies" are the places where one or more natural mineral waters emerge suitable for the practice of *thermalism*, and *thermalism* is defined in the Decree-Law n°. 142/204 of June 11 as being "the use of natural mineral water, deep circulation water characterized by the stability of its chemical, physicochemical and microbiological properties, and of other complementary means for the purposes of prevention, therapy, rehabilitation or just well-being".

With regard to natural mineral water hardness, this property indicates the presence of alkaline earth metals. On this basis, natural mineral waters may be classified as *very soft* (0–100 mg/L of $CaCO_3$), *soft* (100–200 mg/L of $CaCO_3$), *hard* (200–300 mg/L of $CaCO_3$) or *very hard* (>300 mg/L of $CaCO_3$) (*In*: Albertini et al. 2007). The so-called total hardness (TH) of a natural mineral water is defined as the sum of the concentrations of Ca, Mg and other multivalent cations.

Regarding molecular concentration of natural mineral waters, this property depends on the number of molecules dissolved in a certain water volume, and it is proportional to osmotic pressure. Based on molecular concentration/osmotic pressure, natural mineral waters can be classified into three categories:

1. *Hypertonic* – molecular concentration higher than the blood molecular concentration
2. *Isotonic* – molecular concentration equal to the blood molecular concentration
3. *Hypotonic* – molecular concentration lower than the blood molecular concentration

Regarding radioactivity, a property that has already been valued in therapeutic terms and today is devalued, Teixeira (2015) presents the following classification of natural mineral waters:

1. *Non-radioactive waters* – when the radon content (Rn) is less than 2 mμC.L^{-1}
2. *Radioactive waters* – when the radon content is between 2 mμ.L^{-1} and 5 mμC.L^{-1}
3. *Highly radioactive waters* – when the radon content is higher than 5 mμC.L^{-1}

In Portugal, it is in the central region, particularly in lands where uraniferous mineralizations occur, that the natural mineral waters present higher radioactivity.

Gálvez et al. (2018) report several randomized clinical trials which have provided significant long-term beneficial symptom-related effects of radon balneotherapy in the treatment of rheumatic diseases, lasting up to 9 months post-intervention. Compared to radon-free treatments, radon balneotherapy was superior in terms of pain relief, function improvement, reduction in anti-inflammatory and analgesic drug consumption and persistence of these benefits over a longer term (Franke et al. 2000, 2007a, b; Annegret and Thomas 2013; Falkenbach et al. 2005).

As a concluding note, in Portugal, little scientific developments have been published in the last years regarding the use of natural mineral water for therapeutic purposes in thermal health resorts. What it is known so far is still much based on empiricism. A few studies and publications have been carried out and issued mainly produced by scholars and health professionals (Diegues and Martins 2010; Cantista 2011, 2017; Rebelo 2012; Araújo and Coutinho 2012; Coutinho et al. 2015; Pereira 2015; Hipólito-Reis 2016; Gomes 2006, 2012, 2014, 2017, 2018; Silva and Dinis 2017).

Naturally, any clinical research in medical hydrology should involve the contribution of the physicians with competence in medical hydrology who provide medical counselling, prescribe treatments and do patients' surveillance in thermal health resorts. Also, the initiative of research projects would be one's duty of those physicians.

14.4 Therapeutic Vocations of Mineral Thermal Waters Used in Health Resort Medicine in Portugal

Regarding this theme, and in relation to the Portuguese thermal waters, in Portuguese literature, the articles by Teixeira (1990, 1997, 2010, 2012a, b, 2015, 2016a, b, 2017) stand out. According to this author, on the proposal of the Portuguese National Commission of the thermalism (already extinct), was published in the DR (Diário da República) of May 23, 1989, the Joint Order of the Ministries of Health and of Commerce and Tourism of April 5, 1989, that, in relation to the thermal resorts or spas then in operation, fixed the maximum of four therapeutic vocations. This classification was based on the traditions of each spa, but mainly on the physicochemical composition of the respective natural mineral waters, irrespective of whether more objective and scientific criteria could be considered in the future.

Decree n°142/2004 of June 11 refers the need to consider that the therapeutic indications of the Portuguese spas and the corresponding clinical (medical-hydrological) trials should have a scientific basis, what is now underway for a limited number of spa resorts.

The therapeutic indications of the natural mineral waters used in the baths of spa resorts, according to their physicochemical specificities, may include some of the following diseases or disorders: metabolic-endocrine, blood, nervous, circulatory, respiratory, digestive, nephro-urinary, skin, rheumatic and musculoskeletal.

The therapeutic indications attributed to the natural mineral waters used in the Portuguese thermal or health resorts are approved by an Order of the Ministry of Health after recognition of the DGS (Direção-Geral de Saúde) on the proposal of the Technical Evaluation Commission (CAT), which already approved till now the following medical and hydrological studies: Almeida (Guarda), Longroiva (Meda), Cró (Sabugal), Unhais da Serra (Covilhã), Águas de São Tiago (Penamacor), São Lourenço (Carrazeda de Ansiães), Moimenta (Terras de Bouro), Terronha (Vimioso), S. Miguel (Fornos de Algodres), Bicanho (Soure), Murtas (Amarante), Carlão (Murça) and Caldelas (Amares).

More than 30 of the resorts above referred to have already been approved as health resort medicine spas, and most of them utilize or can utilize sulphurous natural mineral waters.

For the time being, the therapeutic vocation of healing mineral thermal waters is a function of their physical-chemical and chemical properties, which allow us to establish, for example, the type of healing mineral waters, highlighting the following five types, which concern and discussion is particularly limited to Portugal:

1. Bicarbonate waters
2. Chloride waters
3. Sulphate waters
4. Hypomineralized or hyposaline waters
5. Sulphurous waters (already being discussed in a general and comprehensive way in topic 13.1.1 of this book; they continue being discussed in Chap. 15 of this book)

Barbosa (2017) reports that, in 2016, the number of users of therapeutic treatments in the Portuguese thermal resorts or spas was about 40,000 and that the user has the average age of 65–74/+75 years and that the number of wellness users was about 74,000 with an average age of 35–44/45–54. In 2016, the billing for therapeutic and beautician treatments amounted to 14 million euro, with an average invoice per customer of 285 euro. The same author refers to the therapeutic areas most frequented in the Portuguese thermal resorts or spas: rheumatological and musculoskeletal disorders, 62.1%; changes in airways, 29.1%; changes in metabolism, 2.9%; changes in circulatory system, 1.6%; alterations of digestive tract, 1.3%; dermatological alterations, 0.8%; others, 2.2%. The natural mineral water used in thermal resorts besides thermal and mechanical properties has specific physical-chemical properties of paramount importance for therapeutic applications – crenotherapy.

Below some considerations are produced regarding the therapeutic roles of natural mineral waters of different chemistry.

14.4.1 Bicarbonate Natural Mineral Waters

In bicarbonate waters, from the chemical point of view, the anions bicarbonate (HCO_3^-) or carbonate (CO_3^{2-}) and the cations calcium (Ca^{2+}) or sodium (Na^+) predominate. From the therapeutic point of view, according to Teixeira (2012a, b, 2017), they are distinguished by their antacid or digestive alkalinizing capacity, particularly when ingested in fasting, i.e. in an empty stomach, the reason why in small and repeated doses they can be used mainly for the treatment of affections of the gastroduodenal tract with hyperacidity and hypermotility, and hepatovesicular. As a matter of fact, bicarbonate ions are the body's most important buffer against acidity. Recommended daily doses (RDD) should not exceed 1000–1200 ml, subdivided into 5–6 doses of 100–200 ml. Still according to Teixeira (2012a, b, 2017), in the northern region of Portugal, there are strongly mineralized bicarbonate waters in Chaves, Vidago, Pedras Salgadas and Melgaço, all strongly carbogaseous. In the case of being calcium and magnesium rich, they may have some sedative activity on neuromuscular excitability and synaptic transmission, as well as some effect on arteriolar, capillary and venous vasodilation, particularly when associated with direct carbogaseous activity through baths.

In summary, the main vocations/therapeutic indications of bicarbonate waters will be disorders of the digestive system (gastric, with hyperacidity, hypermotility and hyposecretion; intestinal, with hypersecretion and hypermotility (plus calcium); and hepatovesicular, with chloride and/or sulphate ones), some metabolic disorders (obese, gout, diabetes) and some disorders of the urinary tract (particularly uric lithiasis due to the possibility of urine alkalinization). Recommended daily doses (RDD) should not exceed 1000–1200 ml, subdivided into 5–6 doses of 100–200 ml. Still according to Teixeira (2012a, b, 2017), in the northern region of Portugal, there are strongly mineralized bicarbonate waters in Chaves, Vidago, Pedras Salgadas and Melgaço, all strongly carbogaseous. Recommended daily doses (RDD) should not exceed 1000–1200 ml, subdivided into 5–6 doses of 100–200 ml.

According to Teixeira (2012a, b, 2017), in the northern region of Portugal, there are strongly mineralized bicarbonate waters in Chaves, Vidago, Pedras Salgadas and Melgaço, all strongly carbogaseous.

14.4.2 Chloride Natural Mineral Waters

In chloride waters, anion chloride (Cl^-) and cation sodium (Na^+) predominate, hence they are called sodium chlorates, although they may contain significant contents of other ions, HCO_3^-, SO_4^{2-}, Ca^{2+} ... therapeutic vocations.

Teixeira (2012a, b, 2017) reports that when mineralization is low (less than physiological saline mineralization), the chloride water can be ingested, thus provoking secretory, motile and trophic stimulants at the gastrointestinal and hepatovesicular levels and, consequently, interfere in the metabolic and hydroelectrolytic processes.

Topical applications, under the form of baths, showers, irrigations and inhalations, have either a healing effect or a resolutory and anti-inflammatory stimulating effect, that is the highest when the chloride content is the highest too. Thus, the main therapeutic vocations are digestive, dermatological, gynaecological, respiratory, rheumatic and musculoskeletal affections.

In oral intake, doses should be carefully adapted to individual tolerance, starting at 50–60 ml two to three times a day in the morning and fasted at 15–30 min intervals, doses that will be increased up to a maximum of 180 ml.

Also, according to Teixeira (2012a, b, 2017), in Portuguese spas, chloride sodium waters are rare, being represented in the northern region by the spa of S. Jorge which water is sulphurous too; other chloride waters occur in the central region of the country, in Caldas da Rainha, Vimeiro, Cucos and Estoril.

14.4.3 Sulphate Natural Mineral Waters

Sulphate anion (SO_4^{2-}) predominates in sulphate waters, as well as sodium (Na^+), calcium (Ca^{2+}) or magnesium (Mg^{2+}) cations. In balneology, waters containing at least 1200 mg/L of sulphate ion (SO_4^{2-}) are referred to as “sulphate waters”. Sulphate waters have a residual taste of bitter, more pronounced when they are magnesian.

Sulphate waters in balneotherapy are mainly used in the management of gastrohepatological and biliary conditions in the form of drinking cures or hydropinic therapies (Fraioli et al. 2010; Mennuni et al. 2014; Bothe et al. 2017). Due to its hypertonicity and specific mineralization, the sulphated waters are stimulants of the digestive sections, namely pancreatic, hydrocholeretic and cholecystokinetic, being laxatives or purgatives, properties less evident in the sulphated calcium waters (facilitating greater ingestion) than in the sulphated sodium.

According to Teixeira (2012a, b, 2015, 2017), the main therapeutic vocations of calcium sulphate waters are the digestive affections, metabolic-endocrine affections favouring urinary elimination (hyperuricemia and renal lithiasis) and diuresis (decreasing arterial hypertension); the therapeutic vocations of sulphated sodic and magnesian waters include the affections of the digestive pathways (vesicular dyskinesias, such as laxatives and purgatives). Depending on the individual tolerance and body weight of the patient, the dose to be taken begins with 50–60 ml in the morning and fasted, repeated three times at 20–30 min intervals, after which the dose may rise to a maximum of 120–180 ml.

In Portugal, there are sulphate waters in Termas da Curia (sulphate calcic and magnesian water) and Monte Real (sulphate calcic water). The water of the spa of Caldas da Rainha is of the mixed type, besides being sulfated it is chloridated and sulfurous too.

14.4.4 Hypomineralized Natural Mineral Waters

Hypomineralized or hyposaline waters are characterized by low total mineralization, but some specific components such as iron, silica and fluoride can justify specific names (ferruginous if rich in Fe, silicate if rich in silica, and fluoridate if rich in fluoride) and equally specific therapeutic vocations.

The therapeutic indications of the hypomineralized water depend on the chemical composition, but it is the affections of the urinary tract, some metabolic-endocrine affections and the liver diseases most valued, particularly by the action of the diuretic effect, preventing the urinary precipitates of oxalates, phosphates, carbonates and urates. Secondary effects of hypomineralized waters are almost inexistent. The doses to be used depend a lot on the pretended effect. As a rule, 120 ml and 3–5 times/day doses are recommended, but they may increase to doubling.

In Portugal, among the hypomineralized waters, the thermal water of Luso (moderately silicate, 19–11 mg/L), the thermal water of Monfortinho (significantly silicate, 18 mg/L) and the thermal water of Vale da Mó (ferruginous and somehow bicarbonate) deserve particular references.

14.4.5 Sulphurous Natural Mineral Waters

Sulphurous natural mineral waters will be discussed in a general and comprehensive way in Chap. 15 of this book. These waters have unpleasant odour and taste. In Portugal, all sulphurous natural mineral waters have low mineralization (except Caldas da Rainha thermal water). The sulphur in natural mineral waters will exert its activity directly on the skin and mucous membranes. However, in addition, because it is well and quickly absorbed through the digestive, respiratory and skin routes, it reaches the circulatory current in significant concentrations and is distributed throughout the body, interfering with practically all oxidation-reduction processes, thus manifesting its antitoxic, anti-anaphylactic, desensitizing, metabolic stimulant, vascular stimulant and cell trophism potential, with consequent regulation of vascular permeability, actions that are particularly evident at the respiratory and osteoarticular level, particularly cartilage tissue and synovial fluid.

14.5 Secondary Effects, Contraindications and Risks of Thermal Therapeutics

All types of natural mineral water used in therapy or thermal cure are not free from side effects and risks. Teixeira (2009, 2015, 2017) refers to the side effects and risks of bicarbonate, chlorinate, sulphate and sulphurous waters and considers practically non-existent side effects and risks in the case of hypomineralized waters.

Martin Megias (2015) reports several negative aspects of the thermal cure, intolerances or adverse reactions and contraindications related to the thermal cure, with the disease and its evolution, with the state of health of the patient.

In the hydropinic thermal cure, the use of water rich in sodium (Na) in hypertensive patients and with cardiovascular and renal complications is discouraged, the use of iron-rich water in patients suffering from hemosiderosis or hemochromatosis and the use of water rich in calcium in patients with lithiasic tendencies. Depending on of the topical application method, the use of water with high temperature in moderate to severe venous insufficiencies and the use of water with high pressure it is not advised in patients suffering from severe osteoporosis.

14.6 Thermal Techniques: Internal Administration and External Application

The thermal techniques as defined by the law (Decree n° 142/2004 of June 11) are:

> The set of means that make use of a natural mineral water and its derivatives (gas, mud, etc.) aided or not by complementary techniques, for the purposes of prevention, therapeutics, rehabilitation and well-being.

Thermal techniques comprise general techniques (internal administration or external application) and special techniques (aiming at obtaining a local effect, resulting from internal administration or external application).

Teixeira (2015, 2017) describes in detail the various techniques used for internal administration (oral ingestion of natural mineral water or hydropinics, injection of natural mineral water, administration via colorectal for absorption of chemical elements) and for external administration (baths, showers, vapours, peloids, etc.).

In internal application, the most common technique is the oral ingestion of water, and all types of natural mineral waters can be ingested, although some due to smell and taste in the case of sulphurous or hydrogen sulphide waters, or others due to high mineralization with effect in the case of chlorinated and sulphated water are difficult to drink. Hydropinic therapy or drinking cure is the name applied to the controlled oral ingestion of mineral-medicinal water.

In external application, the therapeutic effect may result from three groups of factors: hydromechanical, hydrothermal and hydrochemical.

14.7 Monitoring of the Quality of Natural Mineral Water Utilized in Thermal Balnearies

All the natural mineral waters (NMW) used for therapeutic purposes in thermal establishments must be continuously monitored in order to ensure that the regulatory quality criteria are established, and that the requirements verified and approved by the qualified authorities are the appropriate ones. For example, ESPA (European Spas Association) in a General Assembly held in 2006 in the spa of São Pedro do Sul adopted quality criteria for healing waters used in thermal establishments or spas.

The healing waters are extracted from natural springs or from more or less deep catchments, naturally located near the spas. Due to their chemical and physicochemical properties, they produce therapeutic effects that can be used in prevention, cure and rehabilitation. Its effectiveness is demonstrated by balneological experience and medical recognition.

A curative water must meet physicochemical, chemical and microbiological requirements.

Table 14.3 shows the minimum chemical requirements proposed by ESPA for thermal healing waters.

Due to natural causes, both physicochemical properties (temperature, pH, electrical conductivity, total dry matter and dissolved gases) and chemical properties of the mineral water (content of major elements cations and anions, trace element content, and organic substances content) may show small variations or better fluctuations. Therefore, the mentioned properties should be monitored periodically in the thermal centres. ESPA (2006) recommends chemical analyses every 10 years.

Table 14.3 Minimum chemical requirements for healing natural mineral waters

Parameters	mgL^{-1}	$mnmolL^{-1}$
Calcium (Ca^{2+})	500	12.5
Magnesium (Mg^{2+})	150	6.2
Ferrous iron (Fe^{2+})	20	0.2
Lithium (Li^{+})	2	0.29
Sulphate (SO_4^{2-})	1200	12.5
Bicarbonate (HCO_3^{-})	1300	21.3
Iodide (I^{-})	1	0.01
Fluoride (F^{-})	1	0.05
Sulphur (HS^{-}, H_2S, HS^{x-})	1	0.03
Carbon dioxide (CO_2)	1000	22.5
Radon (Rn)	666 Bq/L	–
Salt water	8.5 g Chlorides	–
Natural mineral water	Natural temperature	<20 °C

In Portugal, the DGS-MS/Direcção-Geral da Saúde-Ministério da Saúde (DGS-MS 2011), which established the Norms and Criteria for Thermal Research, recommends monthly analyses.

Rebelo et al. (2014) studied the hydrochemistry of 28 Portuguese natural mineral waters, many of which were used in thermal spas for therapeutic purposes, sampled at springs/boreholes and determined 15 physical and chemical parameters, T (temperature), pH, EC (electric conductivity), TDS (total dissolved solids content), HCO_3^-, F^-, Cl^-, NO_3^-, SO_4^{2-}, Na^+, K^+, Ca^{2+}, Mg^{2+}, Si^{4+} and S, and 19 parameters relative to the chemical elements, minor and trace, Al, As, B, Ba, Br, Cr, Cs, Cu, Fe, Li, Mn, Mo, Rb, Se, Sr, U, W, V and Zn.

From the study carried out, whose first objective was to be able to use these waters in the peloid composition, the hydrogeochemical variability and singularity of these waters stand out, classified into four hydrochemical groups conditioned by hydrogeological environments (magmatic, metamorphic and sedimentary):

Group A – $Ca\text{-}SO_4$	*Group B* – $Ca/Mg\text{-}HCO_3$
Group C – Na-Cl	*Group D* – $Na\text{-}HCO_3$.

The healing water must be sanitary safe, and monitoring requires periodic microbiological testing. ESPA (European Spas Association) refers to microorganisms (coliforms, *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococci faecal*, sulphite-reducing spore-forming *anaerobic bacilli*, number of colonies at 20 °C and 37 °C and *Legionella* spp.) as well as the microbiological tests to be performed, however minimum permissible values. ESPA states that chemical and microbiological analyses must be carried out on samples taken, both at the emergence site and at the place where the water is used.

Morais and Costa (2012) produced an interesting paper on the microbiology of natural mineral waters (NMW) which is dependent upon the hydrogeology and microbial ecology of deep-seated underground water reservoirs.

Natural mineral waters (NMW) have to be wholesome, i.e. they do not require previous treatment or disinfection that could modify or eliminate their biological constituents as happens with treated tap water. Hence, the microbiological natural constituents of NMW would remain unchanged.

So far, in the European Union countries, no diseases and epidemics are known relative to the consumption of NMW, since they fulfil the European microbiological guidelines. The European Council Directive 98/83/EC (1998) regulates both microbiological and chemical sanitary safety, of human consuming water. Both the number and concentration of contaminants that could put at risk the human health are taken into account in any risk evaluation.

In the USA the EPA has established for risk evaluation the guideline of 10^{-4} (one infection/year for 10,000 consumers would be acceptable for diseases acquired through the consumption of potable water, value around the annual real infection risk in the USA (4×10^{-3}) (Gerba 2000).

Natural mineral waters are regulated by the European Council Directive 80/777/EEC (EC 1980). At the source and at the selling date, NMW should be free of parasites and pathogens, requisites different of those required for tap water.

One final and short reference to the project "Hidrogenoma: A New Strategy for NMW" of the DGEG (Direcção-Geral de Energia e Geologia), still going on but already reaching the final phases of the project. About 80 Portuguese NMW used in balneotherapy and drinking bottled water were studied during 2.5 years in order to get scientific data regarding their previously assumed specific microbiomes and potential applications. It has been found out a strong correlation between NMW physicochemical specificities. NMW therapeutic vocations could be scientifically defined, and the expiration date of bottled water could be defined in accordance with water characteristics. Expectations are great.

In Portugal, the DGS-MS (Direção-Geral Saúde-Ministério da Saúde) in the Norms and Criteria for Thermal Research published in 2011 recommends weekly carried out microbiological analyses (DGS-MS 2011).

Table 14.4 shows the recommended maximum values for the pathogenic microorganisms established by IRJ/MS (Ricardo Jorge Institute/Ministry of Health) (2014)

Table 14.4 Recommended maximum values of pathogen microorganisms present in natural mineral water utilized in thermal establishments Instituto Nacional Dr. Ricardo Jorge, Ministério da Saúde, Portaria 1220/2000 of December 29

	Maximum recommended values	
Parameters	By ingestion and in contact with mucouses	By external via
Viable microorganisms at 22 °C	20 ufc/ml	100 ufc/ml
Viable microorganisms at 37 °C	5 ufc/ml	20 ufc/ml
Legionella pneumophila	Not detected/l	Not detected/l
Legionella spp. (non-pneumophila)	100 ufc/l	100 ufc/l

for the Water Healing of Portuguese Terrestrial Establishments, either when the water is ingested and is in contact with the mucous membranes or when the water is applied topically. The aforesaid values are contained in Ordinance 1220/2000 of December 29.

References

Abe K, Kimura H (1996) The possible role of hydrogen sulfide as an endogenous neuromodulator. J Neurosci 16:1066–1071

Abu-Shakra M, Mayer A, Friger M, Harari M (2014) Dead Sea mud packs for chronic low back pain. Isr Med Assoc J 16:574–577

Acciauiuoli LMC (1952) Le Portugal Hydromineral, vol 1. Direcção Geral de Minas e dos Serviços Geológicos, Lisboa

Albertini MC, Dachá M, Teodori L, Conti ME (2007) Drinking mineral waters: biochemical effects and health implications – the state-of-the-art[CG1]. Int. J. Environmental Health, Vol. 1, No. 1

Altan L, Bingol U, Aslan M, Yurtkuran M (2006) The effect of balneotherapy on patients with ankylosing spondylitis. Scand J Rheumatol 35:283–289

Altman N (2000) Healing springs: the ultimate guide to taking the waters. Simon & Schuster, 336 pp.

Altman N (2002) Sacred water. Paulist Press, 295 pp.

Agishi Y, Miyaji M, Shimizu T (2010) Impact of salt in balneo- and thalassotherapy in Japan. In: proceedings of the international conference; international congress. Spa therapy with saline waters in health resorts. Österr Z Phys Med Rehabil 20:60–61

Annegret F, Thomas F (2013) Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomized, multi-centre IMuRa trial. Rheumatol Int 33:2839–2850

Antonnelli A, Donelli D (2018) Effects of balneotherapy and spa therapy on levels of cortisol as a stress biomarker: a systematic review. Int J Biometeorol 62(6):913–924

Araújo A, Coutinho P (2012) Thermal therapy in health: categorization of therapeutic indications for natural mineral waters in the region of Beira interior of Portugal. Balnea-Anales de Hidrologia Médica 6:455–456

ATP (Associação das Termas de Portugal) (2009) Manual de Boas Práticas nos Estabelecimentos Termais, 84 pp. Contributions of: Cardoso Oliveira L, Frederico T, Martins de Carvalho JM, Monteiro C, Cantista P, Santos Silva AJ, Coutinho C, Antunes da Silva M, Pinto Barbosa J

Azevedo C, Vasconcelos L (1995) Termas Portuguesas. Edições INAPA, Lisboa, 160 pp.

Bálint GP, Buchanan WW, Adám A, Ratkó I, Poór L, Bálint PV, Somos E, Tefner I, Bender T (2007) The effect of the thermal mineral water of Nagybaracska on patients with knee joint osteoarthritis-a double blind study. Clin Rheumatol 26:890–894. https://doi.org/10.1007/s10067-006-0420-1

Balogh Z, Ordögh J, Gász A, Német L, Bender T (2005) Effectiveness of balneotherapy in chronic low back pain: a randomized single-blind controlled follow-up study. Forsch Komplementarmed Klass Naturheilkd 12:196–201

Barbosa JP (2017) Situación en Portugal de las termas y su experencia en Peloterapia. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, B alneario El raposo, Badajoz, España, 77

Bazzichi L, DaValle Y, Rossi A, Giacomelli C, Sernissi F, Giannaccini G, Betti L, Ciregia F, Giusti L, Scarpellini P, Dell'Osso L, Marazziti D, Bombardieri S, Lucacchini A (2013) A multidisciplinary approach to study the effects of balneotherapy and mud-bath therapy treatments on fibromyalgia. Clin Exp Rheumatol 31:S111–S120

Beer AM, Junginger H, Lukanov J, Sagorchev P (2003) Evaluation of the permeation of peat substances through human skin in vitro. Int J Pharm 253:169–175

Bellometti S, Fabbri B (2010) Effect of mud pack in fibromyalgia. Focus Altern Complement Ther 5. https://doi.org/10.1111/j.2042-7166.2000.tb02339.x

Bellometti S, Galzigna L (1999) Function of the hypothalamic adrenal axis in patients with fibromyalgia syndrome undergoing mud-pack treatment. Int J Clin Pharmacol Res 19:27–33

Bellometti S, Giannini S, Sartori L, Crepaldi G (1997a) Cytokine levels in osteoarthrosis patients undergoing mud bath therapy. Int J Clin Pharmacol Res 17:149–153

Bellometti S, Cecchettin M, Galzigna L (1997b) Mud pack therapy in osteoarthrosis: changes in serum levels of chondrocyte markers. Clin Chim Acta 268:101–106. https://doi.org/10.1016/S0009-8981(97)00171-X

Bellometti S, Poletto M, Gregotti C et al. (2000) Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients. Int J Clin Pharmacol Res 20:69–80

Bellometti M, Poletto C, Gregotti P, Richelmi F, Berté (2002) Mud bath therapy influences nitric oxide. J Eur Acad Dermatol Venereol,16(3)

Bellometti S, Gallotti C, Pacileo G et al (2007) Evaluation of outcomes in SPA-treated osteoarthrosic patients. J Prev Med Hyg 48(1):1–4

Bellometti S, Gallotti C, Pacileo G, Rota A, Tenconi MT (2007) Evaluation of outcomes in SPA-treated osteoarthrosic patients. J Prev Med Hyg 48(1):1–4. https://doi.org/10.15167/2421-4248/jpmh2007.48.1.81

Bełtowski J (2015) Hydrogen sulfide in pharmacology and medicine: an update. Pharmacol Rep 67:647–658

Benczúr G (1939) Gyakorlati Balneologia és Klimatologia

Bender T, Bálint PV, Bálint GP (2002) A brief history of spa therapy. Ann Rheum Dis 61:949–950

Bender T, G. Bálint, Z. Prohászka, P. Géher, Tefner IK (2014) Evidence-based hydro- and balneotherapy in Hungary - A systematic review and meta-analysis. Int J Biometeorol 58:311–323

Benedetti S, Pagliari S, Benvenuti F, Marini D, Galli T, Oliva F, Lazzari P, Canestrari F (2007) Antioxidative effects of sulphurous water from Macerata Feltria thermal resort in patients with osteoarthritis. Prog Nutr 9:46–52

Benedetti S, Benvenuti F, Nappi G, Fortunati NA, Marino L, Aureli T, De Luca S, Pagliarani S, Canestrari F (2009) Antioxidative effects of sulfurous mineral water: protection against lipid and protein oxidation. Eur J Clin Nutr 63:106–112

Bhatia M (2015) H2S and inflammation: an overview. Handb Exp Pharmacol 230:165–180

Boisseuil D (2015) La cure thermale dans l’Italie de la fin du Moyen Âge et du debut du XVIe siècle. In: Scheid J, Nicoud M, Boisseuil D, Coste J (dirs) Le thermalisme. Approches historiques et archéologiques d’un phenomène culturel et médical, Paris, pp 105–122

Bos EM, Van Goor H, Joles JA, Whiteman M, Leuvenink HG (2015) Hydrogen sulfide: Physiological properties and therapeutic potential in ischaemia. Br J Pharmacol 172(6):1479–1493. https://doi.org/10.1111/bph.12869

Bothe G, Coh A, Auinger A (2017) Efficacy and safety of a natural mineral water rich in magnesium and sulphate for bowel function: a double-blind, randomized, placebo-controlled study. Eur J Nutr 56:491–499

Branco M, Rego NN, Silva PH, Archanjo IE, Ribeiro MC, Trevisani VF (2016) Bath thermal waters in the treatment of knee osteoarthritis: a randomized controlled clinical trial. Eur J Phys Rehab Med 52(4):422–430

Brockow T, Schiener R, Franke A, Resch KL, Peter RU (2007a) A pragmatic randomized controlled trial on the effectiveness of low concentrated saline spa water baths followed by ultraviolet B (UVB compared to UVB only in moderate to severe psoriasis). J Eur Acad Dermatol Venereol 21:1027–1037. https://doi.org/10.1111/j.1468-3083.2007.02152.x

Brockow T, Schiener R, Franke A, Resch KL, Peter RU (2007b) A pragmatic randomized controlled trial on the effectiveness of highly concentrated saline spa water-baths followed by UVB compared to UVB only in moderate to severe psoriasis. J Altern Complement Med 13:725–732. https://doi.org/10.1089/acm.2007.7099

Burguera EF, Vela-Arnero A, Magalhães J, Meijide-Failde R, Blanco FJ (2014) Effect of hydrogen sulfide sources on inflammation and catabolic markers on interleukin 1β–stimulated human articular chondrocytes. Osteoarthritis Cartilage 22:1026–1035

Calado CMA (1988) O quimismo das águas sulfúreas portuguesas. Estudos, Notas e Trabalhos. Serviço de Fomento Mineiro 30:37–49

Calado CMA (2001) A ocorrência de água sulfúrea alcalina no Maciço Hespérico: Quadro Hidrogeológico e Quimiogénese. Universidade de Lisboa. Phd thesis

Cantarini L, Leo G, Giannitti C, Cevenini G, Barberini P, Fioravanti A (2007) Therapeutic effect of spa therapy and short-wave therapy in knee osteoarthritis: a randomized, single blind, controlled trial. Rheumatol Int 27:523–529

Cantista P (2011) O termalismo em Portugal. Anales de Hidrologia Médica 2008–2010(3):79–107

Cantista APP (2016) Medicina termal: a realidade Portuguesa e a Actualidade Internacional. Factores de Risco, Revista da Sociedade Portuguesa de Cardiologia n°41, 66–78.

Carbajo JM, Fernández-Torán MA, Corvillo I, Aguilera L, Meijide R, Carretero MI, Maraver F (2014) Biophysical skin effects of extemporaneous peloids from "Hervideros de Cofrentes Spa" natural mineral water according to their maturity time. J Jpn Soc Balneol Climatol Phys Med 77:507–508. https://doi.org/10.11390/onki.77.507

Carbajo JM, Maraver F (2017) Sulphurous mineral waters: new applications for health. Evid Based Complement Alternat Med

Carbajo JM, Maraver F (2018) Salt water and skin interactions: new lines of evidence. Int J Biometeorol 62:1345–136. https://doi.org/10.1007/s00484-018-1545-z

Carbajo JM, Ubogui J, Vela L, Maraver F (2018a) Sulphurous minerals waters and psoriasis. Med Nat 12:58–602

Carbajo JM, Ubogui J, Vela L, Maraver F (2018b) Aguas sulfuradas y psoriasis. Med Naturista 12:58–60

Carvalho AH (1955) Estudo analítico de águas termais da ilha de São Miguel (Furnas e Ribeira Grande). Direcção-Geral de Minas e Serviços Geológicos, Lisboa, 112 pp

Carubbi C, Masselli E, Calabrò E et al (2019) Sulphurous thermal water inhalation impacts respiratory metabolic parameters in heavy smokers. Int J Biometeorol 63:1209

Chary-Valckenaere I, Damien Loeuille D, Nicolas Jay N, François Kohler F, Tamisier J-N, Roques C-F, Michel Boulange M, Gay G (2018) Spa therapy together with supervised self-mobilisation improves pain, function and quality of life in patients with chronic shoulder pain: a single-blind randomised controlled trial. Int J Biometeorol 62(6):1003–1014. https://doi.org/10.1007/s00484-018-1502-x

Cheleschi S, Gallo I, Tenti S (2020) A comprehensive analysis to understand the mechanism of action of balneotherapy: why, how, and where they can be used? Evidence from in vitro studies performed on human and animal samples. Int J Biometeorol. c

Ciprian L, Lo Nigro A, Rizzo M, Gava A, Ramonda R, Punzi L, Cozzi F (2013) The effects of spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors. Rheumatol Int 33:241–245

Ciani O, Pascarelli NA, Giannitti C, Galeazzi M, Meregaglia M, Fattore G, Fioravanti A (2017) Mud-bath therapy in addition to usual care in bilateral knee osteoarthritis: an economic evaluation alongside a randomized controlled trial. Arthrit Care Res 69:966–972

Codish S, Abu-Shakra M, Flusser D, Friger M, Sukenik S (2005) Mud compress therapy for the hands of patients with rheumatoid arthritis. Rheumatol Int 25:49–54. https://doi.org/10.1007/s00296-003-0402-4

Constant F, Collin JF, Guillemin F, Boulangé M (1995) Effectiveness of spa therapy in chronic low back pain: a randomized clinical trial. J Rheumatol 22:1315–1320

Contoli M, Gnesini G, Forini G, Marku B, Pauletti A, Padovani A, Casolari P, Taurino L, Ferraro A, Chicca M, Ciaccia A, Papi A, Pinamonti S (2013) Reducing agents decrease the oxidative burst and improve clinical outcomes in COPD patients: a randomized controlled trial on the effects of sulphurous thermal water inhalation. Sci World J 2013:927835

Corvillo L, Varela E, Armijo F et al (2017) Efficacy of aquatic therapy for multiple sclerosis: a systemic review. Eur J Phys Rehabil Med 53(6):944–952

Corvillo L, Armijo F, Álvarez-Badillo A et al (2019) Efficacy of aquatic therapy for neck pain: a systematic review. Int J Biometeorol 64:915. https://doi.org/10.1007/s00484-019-01738-6

Costantino M, Nappi G, Contaldi E, Lampa E (2005) Effectiveness of Sulphur spa therapy in psoriasis: clinical-experimental study. Med Clin Term 18:127–137

Costantino M, Filippelli A, Giampaolo C, Tiano L, Carlucci DM, Coiro V, Rastrelli L (2012) Hypoglycemic and antioxidant activities of sulphureous mineral water. Pharmacologyonline 1:220–226

Coutinho P, Ribeiro MP, Araújo ARTS (2015) Dermatological potential of thermo-mineral waters from Beira Interior region, Portugal. Libro de Actas del Congreso Internacional del Agua -Termalismo y Calidad de Vida / I Symposium Internacional de Termalismo y Calidad de Vida, Ourense (Spain), 23–24 Septiembre de 2015, Campus da Auga, Universidade de Vigo (editor), pp 495–498

Cozzi F, Podswiadek M, Cardinale G, Oliviero F, Dani LBellometti S, Poletto M, Gregotti C et al (2000) Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients. Int J Clin Pharmacol Res 20:69–80

Cozzi F, Podswiadek M, Cardinale G, Oliviero F, Dani L, Sfriso P, Punzi L (2007) Mud bath treatment in spondylitis associated with inflammatory bowel disease e a pilot randomized clinical trial. Joint Bone Spine 74:436–439

Dawe RS, Yule S, Cameron H et al (2005) A randomised controlled caomparison of the efficacy of Dead Sea salt balneophototherapy versus narrowband ultravioleta BH monotherapy for the treatment of chronic plaque psoriasis. Br J Dermatol 153:613–619

DGS-MS (2011) Normas e Critérios para a Investigação Termal. Parte I -–Novas Vocações Terapêuticas/Comprovação do Efeito Terapêutico, 11 pp. Parte II-Investigação nos Estabelecimentos Termais (Exemplificação de Estudos Clínicos com Águas Minerais Naturais), 9 pp

Di Marco AM, De Novellis AM, Carluccio V, Lanuti P et al. (2019) Short-and long-term beneficial effects of beneficial medicinal mineral water administration. Environ Geochem Health. https://doi.org/10.1007/s10653-019-00290-x

Diegues P, Martins V (2010) Águas Termais: Riscos e Benefícios. Direcção-Geral da Saúde.

DiGioia ML, Leggio A, LePera A, Liguori A, Perri A (2006) Occurrence of organic compounds in the thermal sulphurous waters of Calabria, Italy. Chromatographia 63:585–590

Dönmez A, Karagülle MZ, Tercan N, Dinler M, Issever H, Karagülle M, Turan M (2005) SPA therapy in fibromyalgia: a randomized controlled study. Rheumatol Int 26:168–172

EC (1980) Council Directive relating the quality of water intended for human consumption (80/778/EEC). Off J Eur Community L229:11–29

EC (1998) Council Directive relating to the quality of water intended for human consumption (98/83/EEC). Off J Eur Community L330:32–54

Ekmekcioglu C, Strauss-Blasche G, Holzer F, Marktl W (2002) Effect of sulfur baths on antioxidative defense systems, peroxide concentrations and lipid levels in patients with degenerative osteoarthritis. Forsch Komplementarmed Klass Naturheilkd 9:216–220

Elkayam O, Wigler I, Tishler M, Rosenblum I, Caspi D, Segal R, Fishel B, Yaron M (1991) Effect of spa therapy in Tiberias on patients with rheumatoid arthritis and osteoarthritis. J Rheumatol 18:1799–1803

Emmanuel T, Lypaek D, Johansen C, Iversen L (2020) Effect of Dead Sea Climatotherapy on psoriasis: a prospective cohort study. Front Med 18. https://doi.org/10.3389/fmed2020.00083

Erickson HP (2007) Evaluation of the cytoskeletal. Bio Essays. https://doi.org/10.1002/bies.20601

ESPA (2006) European Spas Association. Quality criteria of ESPA

Espejo-Antúnez L, Cardero-Durán MA, Garrido-Ardila EM, Torres-Piles S, Caro-Puértolas B (2013) Clinical effectiveness of mud pack therapy in knee osteoarthritis. Rheumatology (Oxford) 52:659–668

Evcik D, Kavuncu V, Yeter A, Yigit I (2007) The efficacy of balneotherapy and mud-pack therapy in patients with knee osteoarthritis. Joint Bone Spine 74:60–65

Failde RM (2008) El água: Hidratación y Salud. Tribunatermal 12:20–27

Falagas ME, Zarkadoulia E, Rafailidis PI (2009) The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials. Int J Clin Pract 63:1068–1084

Falkenbach A, Kovacs J, Franke A, Jörgens K, Ammer K (2005) Radon therapy for the treatment of rheumatic diseases: review and meta-analysis of controlled clinical trials. Rheumatol Int 25:205–210

Fazaa A, Souabni L, Ben Abdelghani K, Kassab S, Chekili S, Zouari B, Hajri R, Laatar A, Zakraoui L (2014) Comparison of the clinical effectiveness of thermal cure and rehabilitation in knee osteoarthritis. A randomized therapeutic trial. Ann Phys Rehabil Med 57(9–10):561–569. https://doi.org/10.1016/j.rehab.2014.09.007

Feinendegen LE (2005) Evidence for beneficial low level radiation effects and radiation hormesis. Br J Radiol 78(925):3–7. https://doi.org/10.1259/bjr/63353075

Fioravanti A, Perpignano G, Tirri G, Cardinale G, Gianniti C, Lanza CE, Loi A, Tirri E, Sfriso P, Cozzi F (2007) Effects of mud-bath treatment on fibromialgia patients: a randomized clinical trial. Rheumatol Int 27:1157–1161. https://doi.org/10.1007/s00296-007-0358-x

Fioravanti A, Iacoponi F, Bellisai B, Cantarini L, Galeazzi M (2010) Short and long-term effect of spa therapy in knee osteoarthritis. Am J Phys Med Rehabil 89:125–132

Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M (2011) Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int 31:1–8

Fioravanti A, Tenti S, Giannitti C, Fortunati NA, Galeazzi M (2014) Short- and long-term effect of mud bath treatment on hand osteoarthritis: a randomized clinical trial. Int J Biometeorol 58:79–86

Fioravanti A, Karagülle M, Bender T, Karagülle MZ (2017) Balneotherapy in osteoarthritis: facts, fiction, and gaps in knowledge. Eur J Integr Med 9:148–150

Flusser D, Abu-Shakra M, Friger M, Codish S, Sukenik S (2002) Therapy with mud compresses for knee osteoarthritis: comparison of natural mud preparations with mineral-depleted mud. J Clin Rheumatol 8:197–203

Forestier R, Forestier FB, Francon A (2016) Spa therapy and knee osteoarthritis: a systematic review. Ann Phys Rehabil Med 59:216–226

Fraioli A, Menunni G, Petraccia L, Fontana M, Nocchi S, Grassi M (2010) Sulphate-bicarbonate mineral waters in the treatment of biliary and digestive tract diseases. Clin Ter 161:163–168

Fraioli A, Serio A, Mennuni G, Ceccarelli F, Petraccia L, Fontana M, Grassi M, Valesini G (2011) A study on the efficacy of treatment with mud packs and baths with Sillene mineral water (Chianciano Spa Italy) in patients suffering from knee osteoarthritis. Rheumatol Int 31:1333–1340

Fraioli A, Mennuni G, Fontana M, Nocchi S, Ceccarelli F, Perricone C, Serio A (2018) Efficacy of spa therapy, balneotherapy and mud-bath therapy in the management of knee osteoarthritis. a systemic review. BioMed Res Intern 2018:1. https://doi.org/10.1155/2018/1042576

Franke A, Reiner L, Pratzel HG, Franke T, Resch KL (2000) Long-term efficacy of radon spa therapy in rheumatoid arthritis: a randomized sham-controlled study and follow-up. Rheumatology 39:894–902

Franke A, Reiner L, Resch KL (2007a) Long-term benefit of radon spa therapy in the rehabilitation of rheumatoid arthritis: a randomized, multi-Centre IMuRa trial. Rheumatol Int 27:703–713

Franke A, Reiner L, Resch KL (2007b) Long-term benefit of radon spa therapy in the rehabilitation of rheumatoid arthritis: a randomised, double-blinded trial. Rheumatol Int 27:703–713

Gálvez Galve JJ, Peiró PS, Lucas MO, Torres AH, Gil ES, Pérez MB (2012) Quality of life and assessment after local application of sulphurous water in the home environment in patients with psoriasis vulgaris: a randomized placebo-controlled pilot study. Eur J Integr Med 4:e213–e218

Gálvez I, Torres-Piles S, Ortega-Ricón E (2018) Balneotherapy, immune system, and stress response: a hormetic strategy? Int J Mol Sci 19(6):1687

Gálvez I, Torres-Piles S, Ortega-Ricón E (2019) Effect of mud-bath therapy on the innate/inflammatory responses in elderly patients with osteoarthritis: a discussion of recent results and a pilot study on the role of the innate function of monocytes. Int J Biometeorol 64:927. https://doi.org/10.1007/s00484-019-01748-4

Gáti F, Tefner IK, Kovács L, Hodosi K, Bender T (2018) The effects of calcium-magnesium bicarbonate content in thermal mineral water on chronic low back pain: a randomized, controlled follow-up study. Int J Biometeorol 62(5):897–905

Gerba CP (2000) Risk assessment. In: Gerba CP, Maier RM, Pepper IL (eds) Environmental microbiology. Academic Press, London, 557-571 pp.

Ghersetich I, Brazzini B, Hercogova J, Lotti T (2001) Mineral waters: instead of cosmetics or better than cosmetics? Clin Dermatol 19(4):478–482

Giannitti C, de Palma A, Pascarelli NA, Cheleshi S (2017) Can balneotherapy modify microRNA expression levels in osteoarthritis? A comparative study in patients with knee osteoarthritis ugust Int J Biometeorol 61(12):1–6, https://doi.org/10.1007/s00484-017-1420-3

Gomes CSF (2014) Naturotherapies Based on Minerals. Geomaterials 3:1–14

Gomes CSF (2017) Notas sobre Água, Terra, Vida e Saúde. In: Cap. VIII do livro *Águas Minerais Naturais e de Nascente da Região Norte* (coordenação de J.A. Simões Cortez), (edição de Mare Liberum – Editora para a FEDRAVE), pp 285–352

Gomes CSF (2018) Healing and edible clays: a review of basic concepts, benefits and risks. Environ Geochem Health 40:1739–1765. https://doi.org/10.1007/s10653-016-9903-4

Gomes CSF, Silva JBP (2012). Minerais e Peloides no Termalismo. Cap. XIV do livro *Águas Minerais Naturais e de Nascente da Região Centro* (coordenação de J.A. Simões Cortez), (edição de Mare Liberum – Editora para a FEDRAVE), pp 301–379

Gómez JAG, López LAR (2015) Contaminación de las águas termales por *Escherichia Coli* y la aplicación del ozono en su tratamento. Libro de Actas del Congreso Internacional del Agua -Termalismo y Calidad de Vida / I Symposium Internacional de Termalismo y Calidad de Vida, Ourense (Spain), 23–24 Septiembre de 2015, Campus da Auga, Universidade de Vigo (editor), pp 163–167

Gómez CP, Soutelo GS, Mourelle ML, Legido JL (2019) Spa techniques and technologies: from the past to the present. Sustain Water Resour Manag 5:71–81

Gonzales-Barreiro C, Cancho-Grande B, Araujo-Nespereira P, Cid-Fernández JA, Simal-Gándara J (2009) Occurrence of soluble organic compounds in thermal waters by ion trap mass detection. Chemosphere 75:34–47

González Soutelo S (2007a) En los orígenes de los balnearios, spas y centros de talasoterapia. Los establecimientos termales en el mundo antiguo. Parte I. Tribuna Termal 5:55–61

González Soutelo S (2007b) En los orígenes de los balnearios, spas y centros de talasoterapia. Los establecimientos termales en el mundo antiguo. Parte II. Tribuna Termal 6:34–39

Grether-Beck S, Mühlberg K, Brenden H et al (2008) Bioactive molecules from the Blue Lagoon: in vitro and in vivo assessment of silica mud and microalgae extracts for their effects on the skin barrier function and the prevention of skin ageing. Exp Dermatol 17(9):771–779. https://doi.org/10.1111/j.1600-0625.2007.00693

Guérin-Beauvois M, Martin JM (eds) (2007) Bains curatifs et bains hygiéniques en Italie de l'Antiquité au Moyen âge (actes du colloque tenu à Rome les 22 et 23 mars 2004). École française de Rome, Paris

Guidelli GM, Tenti S, De Nobili E, Fioravanti A (2012) Fibromyalgia syndrome and spa therapy: myth or reality? Clin Med Insights Arthritis Musculoskelet Disord 5:19–26. https://doi.org/10.4137/CMAMD.S8797

Guimarães F, Guimarães JL (1954) Hidrologia Médica. Águas Minerais de Portugal, Coimbra

Güngen G, Ardic F, Findikoglu G, Rota S (2012) The effect of mud pack therapy on serum YKL-40 and hsCRP levels in patients with knee osteoarthritis. Rheumatol Int 32:1235–1244

Gutenbrunner C, Bender T, Cantista P, Karagulle MZ (2010) A proposal for a worldwide definition of health resort medicine, balneology, medical hydrology and climatology. Int J Biometeorol 54(5):495–507

Gyarmati N, Kulisch A, Németh A, Bergmann A, Horváth J, Mándó Z, Matán A, Szakál E, Péter TS, Szántó D, Bender T (2017) Evaluation of the effect of Hévíz mud in patients with hand osteoarthritis: a randomized, controlled, single-blind follow-up study. Isr Med Assoc J 19:177–182

Halevy S, Sukenik S (1998) Different modalities of spa therapy for skin diseases at the Dead Sea area. Arch Dermatol 134:1416–1420. https://doi.org/10.1001/archderm.134.11.1416

Halevy S, Giryes H, Friger M, Grossman N, Karpas Z, Sarov B, Sukenik S (2001) The role of trace elements in psoriatic patients undergoing balneotherapy with Dead Sea bath salt. Isr Med Assoc J 3:828–832

Hanzel A, Horvát K, Molics B, Berényi K, Németh B, Szendi K, Varga C (2018) Clinical improvement of patients with osteoarthritis using thermal mineral water at Szigetvár spa-results of a randomized double-blind controlled study. Int J Biometeorol 62:253–259. https://doi.org/10.1007/s00484-017-1446-6

Hipólito-Reis C (2016) Estâncias Termais em Portugal: Prespectiva Histórica. Revista Factores de Risco da sociedade Portuguesa de Cardiologia 41:14–24

Hristakieva E (2005) Climatotherapy in dermatology. Trakia J Sci 3(4):27–31

Huang A, Seité S, Adar T (2018) The use of balneotherapy in dermatology. Clin Dermatol 36:363–368

INRJ (Instituto Nacional Ricardo Jorge) / MS (Ministério da Saúde) (2014) Amostragem e Análise de Legionella em Sistemas de Água, 40 pp.

INRJ/MS (Instituto Nacional Ricardo Jorge) / (Ministério da Saúde) (2014) Amostragem e Análise de Legionella em Sistemas de Água, 40 pp.

Jackson R (1990) Waters and spas in the classical world. Med Hist Suppl 10:1–13

Karagülle Z, Dönmez A (2002) Balneotherapy for fibromyalgia at the Dead Sea. Rheumatol Int 21:210–211

Karagülle M, Karagülle MZ (2015) Effectiveness of balneotherapy and spa therapy for the treatment of chronic low back pain: a review on latest evidence. Clin Rheumatol 34:207–214. https://doi.org/10.1007/s10067-014-2845-2

Karagülle MZ, Karagülle M (2019) Effects of drinking natural hydrogen sulfide (H2S) waters: a systematic review of in vivo animal studies. Int J Biometeorol 64:1011. https://doi.org/10.1007/s00484-019-01829-4

Karagülle MZ, Tütüncü ZN, Aslan O, Basak E, Mutlu A (1996) Effects of thermal Sulphur bath cure on adjuvant arthritic rats. Phys Rehab Kur Med 6:53–57

Karagülle M, Karagülle MZ, Karagülle O, Dönmez A, Turan M (2007) A 10-day course of SPA therapy is beneficial for people with severe knee osteoarthritis. A 24-week randomised, controlled pilot study. Clin Rheumatol 26:2063–2071. https://doi.org/10.1007/s10067-007-0618-x

Karagülle M, Kardeş S, Karagülle O, Dişçi R, Avcı A, Durak İ, Karagülle MZ (2017) Effect of spa therapy with saline balneotherapy oxidant/antioxidant status in patients with rheumatoid arthritis: a single-blind randomized controlled trial. Int J Biometeorol 61:169–180. https://doi.org/10.1007/s00484-016-1201-4

Karagülle M, Kardeş S, Karagülle MZ (2018) Long-term efficacy of spa therapy in patients with rheumatoid arthritis. Rheumatol Int 38:353–362. https://doi.org/10.1007/s00296-017-3926-8

Kardeş S, Karagülle M, Geçmen İ, Adıgüzel T, Yücesoy H, Karagülle MZ (2018) Outpatient balneological treatment of osteoarthritis in older persons: a retrospective study. Z Gerontol Geriatr 52:164. https://doi.org/10.1007/s00391-018-1370-3

Katz U, Shoenfeld Y, Zakin V, Sherer Y, Sukenik S (2012) Scientific evidence of the therapeutic effects of dead sea treatments: a systematic review. Semin Arthritis Rheum 42(2):186–200. https://doi.org/10.1016/j.semarthrit.2012.02.006

Kazandieva J, Grozdev I, Darlenski R, Tsankov N (2008) Climatotherapy of psoriasis. Clin Dermatol 26(5):477–485

Kesiktas N, Karakas S, Gun K, Gun N, Murat S, Uludag M (2012) Balneotherapy for chronic low back pain: a randomized, controlled study. Rheumatol Int 32(10):3193–3199

Klein A, Schiffner R, Schiffner-Rohe J et al (2011) A randomised clinical trial in psoriasis: synchronous balneophototherapy with bathing in a Dead Sea salt solution plus narrowband UVB versus narrowband UVB alone (TOMESA-study group). J Eur Acad Dermatol Venereol 25:570–578

Kopel E, Levi A, Harari M, Ruzicke T, Inger A (2013) Effect of the Dead Sea climatotherapy for psoriasis on quality of life. Isr Med Assoc J 15(2):99–102

Kovács I, Bender T (2002) The therapeutic effects of Cserkeszölö thermal water in osteoarthritis of the knee: a double blind, controlled, follow-up study. Rheumatol Int 21:218–221

Kulisch A, Bender T, Németh A, Szekeres L (2009) Effect of thermal water and adjunctive electrotherapy on chronic low back pain: a double-blind, randomized, follow-up study. J Rehabil Med 41:73–79. https://doi.org/10.2340/16501977-0291

Legido JL, Gómez CP, Mourelle L (2015) Nuevas orientaciones versus aplicaciones clássicas de las águas termales. Libro de Actas del Congreso Internacional del Agua -Termalismo y Calidad de Vida / I Symposium Internacional de Termalismo y Calidad de Vida, Ourense (Spain), 23–24 Septiembre de 2015, Campus da Auga, Universidade de Vigo (editor), pp 99–108

Léauté-Labrèze C, Saillour F, Chêne G (2001) Saline Spa water or combined water and UV-B for psoriasis vs conventional UV-BLessons from the Salies de Béarn randomized study. Arch Dermatol 137(8):1035–1039

Leibetseder V, Strauss-Blasche G, Holzer F, Marktl W, Ekmekcioglu C (2004) Improving homocysteine levels through balneotherapy: effects of Sulphur baths. Clin Chim Acta 343:105–111

Maraver F (ed) (2006) Establecimientos balnearios: Historia, literatura y medicina. Balnea 1:1–186

Maraver F (2008) El agua mineral-medicinal: Una herramienta curativa milenaria. Tribunatermal 11:54–57

Maraver F (2017) Aguas mineromedicinales: Importancia terapéutica. In: Vadémecum de las aguas mineromedicinales de Galicia (Gestal JJ, dir.), 21–30, Universidad de Santiago de Compostela.

Maraver F, Armigo F (2010) Vademecum II de Aguas Mineromedicinales Españolas. Univerdidad Complutense de Madrid, Madrid

Maraver F, Armijo F (2010) Vademécum II de aguas mineromedicinales españolas. Complutense, Madrid

Maraver F, Carbajo JM, Vazquez I, Armijo F (2018a) El papel de los elementos minerales y otros componentes químicos utilizados en medicina termal: Aguas mineromedicinales sulfuradas y cloruradas (Nuevos mecanismos de acción). In: Agua Subterránea, Medio Ambiente, Salud y Patrimonio, Congreso Ibérico, AIH-GE, Salamanca, pp 581–590. ISBN: 978-84-938046-6-4

Maraver F, Carbajo JM, Covillo I, Morer C, Vasquez I, Fernandez-Tóran MA, Armijo F (2018b) Las aguas cloruradas de los balnearios españoles: Aplicaciones e indicaciones. Medicina Naturista 12(2):51–56

Martin Megias AI (2015) Aspectos nefativos de la cura termal. Bol Soc Esp Hidrol Méd 30(2):205–215

Matsumoto S (2018) Evaluation of the role of balneotherapy in rehabilitation medicine. Nippon Med Sch 85(4):196–203. https://doi.org/10.1272/jnms.JNMS.2018_85-30

Matz H, Orion E, Wol R (2003) Balneotherapy in dermatology. Dermatol Ther 16(2):132–140

McGrath JA, Eady RA, Pope FM (2010) Anatomy and organization of human skin. In: Rook A, Burns T (eds) Rook's textbook of dermatology, 8th edn. Wiley-Blackwell, Chichester

Meijide FR (2017) El uso medico de las aguas minerales y productos termales. In: Gimenez-Forcada E (ed) I Jornada de Geología Médica en España. La Geologia médica: Una disciplina emergente. Instituto Geológico y Minero de España, Madrid, pp 29–45

Meijide-Faílde R, Leira M, Torres Vaamonde JE (2015) Estudio del componente biológico de las águas mineromedicinales y termales de Ourense: Burgas y Outariz. Libro de Actas del Congreso Internacional del Agua -Termalismo y Calidad de Vida / I Symposium Internacional de Termalismo y Calidad de Vida, Ourense (Spain), 23–24 Septiembre de 2015, Campus da Auga, Universidade de Vigo (editor), pp 519–524

Mennuni G, Petraccia L, Fontana M, Nocchi S, Stortini E, Romoli M, Esposito E, Priori F, Grassi M, Geraci A, Serio A, Fraioli A (2014) The therapeutic activity of sulphate-bicarbonate-calcium-magnesiac mineral water in the functional disorders of the biliary tract. Clin Ter 165:e346–e352

Moss GA (2010) Water and health: a forgotten connection. Perspect Public Health 130(5):227–232. https://doi.org/10.1177/1757913910379192

Morais PV, Costa MS (2012) Microbiologia das Águas Minerais Naturais. Capítulo VII, pp. 137–182, In: "Águas Minerais Naturais e de Nascente da Região Centro. Simões Cortez JA (coordenador), Mare Liberum (editor). ISBN: 978-972-8046-17-0

Morer C, Roques CF, Françon A, Forestier R, Maraver F (2017) The role of mineral elements and other chemical compounds used in balneology; data from double-blind randomized clinical trials. Int J Biometeorol 61:2159–2173

Mourelle L, Gómez CP (2015) Cosmética Termal: Aplicaciones en el ambito de la salud y la beleza. Libro de Actas del Congreso Internacional del Agua -Termalismo y Calidad de Vida / I Symposium Internacional de Termalismo y Calidad de Vida, Ourense (Spain), 23–24 Septiembre de 2015, Campus da Auga, Universidade de Vigo (editor), pp 389–398

Mudry Ph (2015) Le thermalisme dans l'antiquité. Mais où sont les médicins? In: Scheid J, Nicoud M, Boisseuil D, Coste J (dirs) Le Thermalisme: Approches historiques et archéologiques d'un phenomène culturel et médical. Pigeaud Richard, Paris, pp 65–78

Munteanu C, Munteanu D (2019) Thalassotherapy today. Balneo Research Journal, Romanian Association of Balneology 10(4):440–404

Munteanu C, Munteanu D, Hoteteu M (2014) Balneotherapy and healthy ageing- review. Balneo Resour J 5:62–81

Nakata H (2008) Japan's hot springs part of social, geologic and historic fabric. The Japan Times, 22 January 2008

Nasermoaddeli A, Kagamimori S (2005) Balneotherapy in medicine: a review. Environ Health Prev Med 10:171–179

Naumann J, Sadaghiani C (2014) Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. Arthritis Res Ther 16(4):R141. https://doi.org/10.1186/ar4603

Nunes S, Tamura BM (2012) A historical review of mineral water. Surg Cosmet Dermatol 4:252–258

Odabasi E, Turan M, Erdem H, Tekbas F (2008) Does mud pack treatment have any chemical effect? A randomized controlled clinical study. J Altern Complement Med 14:559–565

Ottaviano G, Marioni G, Staffieri C, Giacomelli L, Marchese-Ragona R, Bertolin A, Staffieri A (2011) Effects of sulfurous, salty, bromic, iodic thermal water nasal irrigations in nonallergic chronic rhinosinusitis: a prospective, randomized, double-blind, clinical, and cytological study. Am J Otolaryngol 32:235–239

Ozkurt S, Donmez A, Karagulle Z, Uzunuglu E, Turam M, Erdogan N (2012) Rheumatol Int 32:1949–1954. https://doi.org/10.1007/s00296-011-1888-9

Özkuk K, Gürdal H, Karagülle M, Barut Y, Eröksüz R, Karagülle MZ (2017) Balneological outpatient treatment for patients with knee osteoarthritis; an effective non-drug therapy option in daily routine? Int J Biometeorol 61:719–728. https://doi.org/10.1007/s00484-016-1250-8

Pereira AIF (2015) tratamentos Termais e Dermatoses: Evidências de Cosméticos Termais como Adjuvantes. MSc Dissertação. Escola Superior de Tecnología da Saúde do Porto, Porto.

Pérez-Fernández MR, Calvo-Ayuso N, Martínez-Reglero C, Salgado-Barreira Á, Muiño López-Álvarez JL (2019) Efficacy of baths with mineral-medicinal water in patients with fibromyalgia: a randomized clinical trial. Int J Biometeorol 63(9):1161–1170. https://doi.org/10.1007/s00484-019-01729-7

Péter I, Jagicza A, Ajtay Z, Boncz I, Kiss I, Szendi K, Kustán P, Németh BV (2017) Balneotherapy in psoriasis rehabilitation. In Vivo 31(6):1163–1168

Pittler MH, Karagülle MZ, Karagülle M, Ernst E (2006) Spa therapy and balneotherapy for treating low back pain: meta-analysis of randomized trials. Rheumatology 45:880–884

Polefka TG, Bianchini RJ, Shapiro S (2012a) Interaction of mineral salts with the skin: a literature review. Int J Cosmet Sci 34:416–423

Polefka TG, Bianchini RJ, Shapiro S (2012b) Interaction of mineral salts with the skin: A literatura survey. Int J Cosmet Sci 34:416–423. https://doi.org/10.1111/j.1468-2494.2012.00731.x
Portaria 1220/2000 – Água Mineral Natural Utilizada nos Estabelecimentos TermaisBathin in a magnesium-rich Dead Sea salt solution improves the skin barrier function, enhances skin hydration and reduces inflammation in atopic dry skin
Portugal-Cohen M, Oron M, Merrik et al (2011) A Dead Sea water-enriched body cream improves the skin severity scores in children with atopic dermatitis. J Cosmet Dermatol Sci Appl 1:71–78
Proksch E, Nissen HP, Bremgartner M, Urquhart C (2005) Bathin in a magnesium-rich Dead Sea salt solution improves the skin barrier function, enhances skin hydration and reduces inflammation in atopic dry skin. Int J Dermatol 44:151–157
Ramalho O (1944) Banhos de Caldas e Águas Minerais (1ª edição de 1875 e última edição de 1944)
Rapolienė L, Razbadauskas A, Mockevicienė D, Varzaitytė L, Skarbalienė A (2019) Balneotherapy for musculoskeletal pain: does the mineral content matter? Int J Biometeorol. Published online. https://doi.org/10.1007/s00484-019-01800-3
Rebelo H (2012) Águas Termais em Portugal: Indicações Terapêuticas e Modos de Utilização. Escola Nacional de Saúde Dr. Ricardo Jorge, Lisboa
Rebelo M, Silva EF, Rocha F (2014) Characterization of Portuguese thermo-mineral waters to be applied in peloids maturation. Environ Earth Sci. Springer. https://doi.org/10.1007/s12665-014-3670-2
Routh HB, Bhowmik KR, Parish LC, Witkowski JA (1996) Balneology, mineral water, and spas in historical perspective. Clin Dermatol 14(6):551–554
Sammama E (2015) Sources chaudes et eau médicale : Un «Thermalisme» Grec? In: Scheid J, Nicoud M, Boisseuil D, Coste J (dirs.) Le thermalisme. Approches historiques et archéologiques d'un phenomène culturel et médical, Paris, pp 13–30
Santos I, Cantista P, Vasconcelos C (2016) Balneotherapy in rheumatoid arthritis – a systematic review. Int J Biometeorol 60(8):1287–1301. https://doi.org/10.1007/s00484-015-1108-5
Sarsan A, Akkaya N, Ozgen M, Yildiz N, Atalay NS, Ardic F (2012) Comparing the efficacy of mature mud pack and hot pack treatments for knee osteoarthritis. J Back Musculoskelet Rehabil 25:193–199
Scheidleder B, Holzer F, Marktl W (2000) Effect of sulfur administration on lipid levels, antioxidant status and peroxide concentration in health resort patient. Forsch Komplementarmed Klass Naturheilkd 7:75–78
Schiener R, Brockow T, Franke A, Salzer B, Peter RU, Resch KL (2007) Bath PUVA and saltwater baths followed by UV-B phototherapy as treatments for psoriasis: a randomized controlled trial. Arch Dermatol 143:586–596. https://doi.org/10.1001/archderm.143.5.586
Schrieber R, Gareis H (2007) Gelatine handbook: theory and industrial practice. Germany, Weinheim
Seite S (2013) Thermal waters as cosmeceuticals: the example of La Roche-Posay thermal spring water. Clin Cosmet Investig Dermatol 6:23–28. https://doi.org/10.2147/CCID.S39082
Selye H (1936) Nature, July 04 1936, 132
Serbulea M, Payyappallimana U (2012) Onsen (hot springs) in Japan -transforming terrain into healing landscapes. Health Place 18(6):1366. https://doi.org/10.1016/j.healthplace.2012.06.020
Shani Jl, Barak S, Levi Dl, Ram MI, Schachner ER, Schlesinger T, Robberecht H, Van Grieken R, Avrach WW (1985) Skin penetration of minerals in psoriatics and guinea-pigs bathing in hypertonic salt solutions. Pharmacological Research Communications, 17(6)
Silva AS, Dinis L (2017) Avaliação da Concentração de Radão nas Águas Minerais Naturais nos Estabelecimentos Termais Portugueses. Ricot (editor). Int J Working Conditions 13: 35–50
Spilioti E, Vargiami M, Letsiou S, Gardikis K, Sygouni V, Koutsoukos P, Chinou I, Kassi E, Moutsatsou P (2017) Biological properties of mud extracts derived from various spa resorts. Environ Geochem Health 39(4):821–833. https://doi.org/10.1007/s10653-016-9852-y
Steinsland S (2012) Transdermal delivery of water-soluble molecules into human skin. PhD thesis, Norwegian University of Science and Technology

Sukenik S, Buskila D, Neumann L, Kleiner-Baumgarten A (1992) Mud pack therapy in rheumatoid arthritis. Clin Rheumatol 11:243–247

Szabó C (2007) Hydrogen sulphide and its therapeutic potential. Nat Rev Drug Discov 6:917–935

Szabó I, Varga C (2019) Finding possible pharmacological effects of identified organic compounds in medicinal waters (BTEX and phenolic compounds). Int J Biometeorol 64:1–7. https://doi.org/10.1007/s00484-019-01808-9

Szucs L, Ratko I, Lesko T, Szoor I, Genti G et al (1989) Double-blind trial on the effectiveness of the Puspokladany thermal water on arthrosis of the knee-joints. J R Soc Health 109:7–9

Tefner IK, Németh A, Lászlófi A, Kis T, Gyetvai G, Bender T (2012) The effect of spa therapy in chronic low back pain: a randomized controlled, single-blind, follow-up study. Rheumatol Int 32:3163–3169

Tefner IK, Gaál R, Koroknai A, Ráthonyi A, Gáti T, Monduk P, Kiss E, Kovács C, Bálint G, Bender T (2013) The effect of Neydharting mud-pack therapy on knee osteoarthritis: a randomized, controlled, double-blind follow-up pilot study. Rheumatol Int 33:2569–2576

Teixeira F (1990) Termas e Saúde. Publ Inst Climat Hidrol Universidade de Coimbra 30:5–17

Teixeira F (1997) Evolução do termalismo médico em Portugal. Publ Inst Climat Hidrol Universidade de Coimbra 35:1–24

Teixeira F (2009). Água, fonte da vida. In: "*À Beira da Água*", Comissão de Coordenação e Desenvolvimento da Região Centro (editor), pp 109–139. ISBN: 978-972-569-160-1

Teixeira F (2010). La utilización de las lamas en Portugal: Passado y Presente. II Congreso Iberoamericano de Peloides, Balneário de Lanjarón. Libro de Resúmenes (Maraver F y Carretero M I, editores), pp 14–15

Teixeira F (2012a) O Termalismo na Região Centro. Capítulo XIII do livro "Águas Minerais Naturais e de Nascente da Região Norte", Simões Cortez JA (Coordenador), Mare Liberum, FEDRAVE (editor), pp 261–300

Teixeira F (2012b) O Termalismo na Região Centro. In: "Águas Minerais Naturais e de Nascente da Região Centro", Coordenador JA Simões Cortez, Ed. Mare Liberum, FEDRAVE, pp 261–300

Teixeira F (2015) O Termalismo na Região Centro. Vol. 30, n° 2, Boletín de la Sociedad Española de Hidrologia Médica, pp 135–170

Teixeira F (2016a) Termalismo terapêutico em Portugal: Presente e perspectivas futuras. Revista Factores de Risco, Sociedade Portuguesa de. Cardiologia 41:26–37

Teixeira F (2016b) Termalismo Terapêutico em Portugal: Presente e Perspectivas Futuras. In: Hidrologia Médica e Termalismo: Pilares de Salutogénese, Factores de Risco, Revista da Sociedade Portuguesa de Cardiologia, n° 41 (July–September), 26–37.

Teixeira F (2017) O Termalismo na Região Norte. Capítulo IV do livro "Águas Minerais Naturais e de Nascente da Região Norte", Simões Cortez JA (Coordenador), Mare Liberum, FEDRAVE (editor), pp 159–193

Tenti S, Cheleschi S, Galeazzi M, Fioravanti A (2015) Spa therapy: can be a valid option for treating knee osteoarthritis? Int J Biometeorol 59(8):1133–1143. https://doi.org/10.1007/s00484-014-0913-6

Torres AH, Garcia-Pellicer MP, Aznar FM (2015) Mejora de calidad de vida en pacientes com patologia venosa tratados protocolizadamente com peloides naturales antioxidantes como coadyuvantes vasculares. Libro de Actas del Congreso Internacional del Agua -Termalismo y Calidad de Vida / I Symposium Internacional de Termalismo y Calidad de Vida, Ourense (Spain), 23–24 Septiembre de 2015, Campus da Auga, Universidade de Vigo (editor), pp 499–512

Tsoureli-Nikita E, Menchini G, Ghersetich I, Hercogova J (2002) Alternative treatment of psoriasis with balneotherapy using Leopoldine spa water. J Eur Acad Dermatol Venereol 16:260–262

Valenzuela MA, Bacaicoa JSM (1984) La Saud por las Águas Termales. EDAF (ed.), Madrid

Valenzuela MA, Bacaicoa JSM (1994) Curas Balneárias y Climáticas: Talassoterapia y Helioterapia. Ed. Univ. Complutense de Madrid, Madrid

Varga C (2012a) Volatile organics in thermal spa waters: active ingredients or environmental toxicants? Thermae Spa Med 2:1–8

Varga C (2012b) Balneoprevention: new approaches. Int J Biometeorol 56:195–197

Varga C (2016) On the proper study design applicable to experimental balneology. Int J Biometeorol 60:1307–1309. https://doi.org/10.1007/s00484-015-1113-8

Vos T, Flaxman AD, Naghavi M et al (2013) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries (1990–2010): a systematic analysis for the global burden of disease study 2010. Lancet 380(9859):2163–2196

Waring RH (2004) Absorption of magnesium sulphate through the skin. School of Biosciences of the University of Birmingham, UK (republished by the Epsom Salt Council)

Wang R (2012) Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev 92:791–896

Wu D, Hu Q, Zhu Y (2016) Therapeutic application of hydrogen sulfide donors: the potential and challenges. Front Med 10:18–27

Yoshioka A, Bando H, Nishikiori Y, Nakanishi A (2019) Recent status of hydrotherapy and balneotherapy with clinical beneficial effects. Int J Complement Alt Med 12(6):217–219

Yücesoy H, Geçmen I, Adıgüzel T, Karagülle M, Karagülle MZ (2019) Efficacy of balneological outpatient treatment (hydrotherapy and peloidotherapy) for the management of chronic low back pain: a retrospective study. Int J Biometeorol 63:351–357

Yurtkuran M, Yurtkuran M, Alp A, Nasircilar A, Bingöl U, Altan L, Sarpdere G (2006) Balneotherapy and tap water therapy in the treatment of knee osteoarthritis. Rheumatol Int 27:19–27

Ziemska J, Szynal T, Mazanska M, Solecka J (2019) Natural medicinal resources and some of their therapeutic applications. Rocz Panstw Zakl Hig 70(4):407–413. https://doi.org/10.32394/rpzh/2019.0093

Chapter 15
Healing Sulfurous Thermal Waters in Health Resort Medicine: Therapies, Indications, and Contraindications

Francisco M. L. Amado and Eduardo A. F. Silva

Abstract This chapter will mainly focus on the general assets and applications of sulfur- or H_2S-bearing thermal mineral waters on a world scale. It deals with basic information on hydrogen sulfide properties, on biological effects, and on the therapies traditionally used in medical hydrology as treatment for skin, respiratory, and musculoskeletal disorders. The authors provide information on additional therapeutic benefits of sulfurous waters in diseases such as myalgia (muscle pain), rheumatic diseases (osteoarthritis, rheumatoid arthritis, fibromyalgia), respiratory diseases (upper and lower respiratory tracts), dermatological/skin diseases, cardiovascular diseases, and other diseases (cancer, wound healing in diabetic patients). Possible side effects or situations of diseases for which sulfurous thermal waters are contraindicated are reported too.

15.1 Basic Information

There are various typologies of mineral thermal waters used in balneotherapy, based on their physical, physicochemical, and chemical properties, mainly emergence temperature, dominating anion and cation species, and mineral concentration, classified as sulfurous, sulfate, bicarbonate, chloride, silicate, etc.

Balneotherapy with mineral waters, particularly with sulfurous waters, has been used in multiple pathophysiological conditions in particular of the cardiovascular, respiratory, endocrine, skeletal muscle, dermatological, gastrointestinal, and genitourinary systems and even neurological disorders (Gálvez et al. 2018). It is usually

---

F. M. L. Amado (✉)
Department of Chemistry, University of Aveiro, Aveiro, Portugal
e-mail: famado@ua.pt

E. A. F. Silva
Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal
e-mail: eafsilva@ua.pt

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_15

considered that the benefits of balneotherapy are multifactorial in nature, involving not only the physicochemical characteristics of mineral waters (e.g., water temperature, chemical composition) but also the various techniques of rehabilitation, nutritional aspects, favorable environment, and medical monitoring (Forestier 2000).

This chapter will mainly focus on the general assets and applications of sulfur thermal mineral waters on a world scale.

15.2 H_2S and Sulfurous Mineral Thermal Waters

Hydrogen sulfide (H_2S) has long been known as a foul-smelling, toxic gas. H_2S is a covalent hydride, is a colorless gas, and is highly soluble in water, with a characteristic rotten egg odor (Table 15.1). In water, the taste and odor thresholds for hydrogen sulfides are estimated to be between 0.05 and 0.1 ppm. The taste and odor threshold for sulfides is about 0.2 ppm (WHO 2000). H_2S is heavier than air, flammable, corrosive, and very poisonous.

Showing a similar geometry to the water molecule, due to the sulfur lower electronegativity than oxygen's, in aqueous solution, H_2S molecule is a weak diprotic acid (Filipovic et al. 2018).

Table 15.1 presents the most relevant characteristics of H_2S.

The presence and stability of H_2S is controlled by several variables such as (a) temperature (T), (b) pH, (c) Eh medium conditions (Lima 2011), and (d) dissolved oxygen concentration (Carbajo and Maraver 2017).

About T it is well known that two H_2S-bearing solutions with similar compositions but with different temperatures will have different H_2S concentrations; the higher the temperature, the lower the concentration of H_2S as a pure gaseous molecule, and the higher the concentration of its salts (Carbajo and Maraver 2017).

The pH variable is important in relation to the H_2S concentrations in an aqueous system (Fig. 15.1). The stable form depends on this parameter as well as the relative concentrations of the species. Sulfur forms change at two critical pHs, pKa = 7.04 and pKa = 11.96. At acidic media, H_2S is the only form of sulfur present. At pH of 7.04, sulfur salts occur at 50% concentration.

Table 15.1 Hydrogen sulfide properties

Appearance	Colorless gas
Molecular formula	H_2S
Molecular weight	34.08
Boiling point	−60.33 °C
Specific weight	0.916 at −60 °C
Vapor pressure	20 atmospheres at 25.5 °C
Fusion point	−85.49 °C
Explosive limits	4.3 to 45%
pH of a saturated aqueous solution	4.5

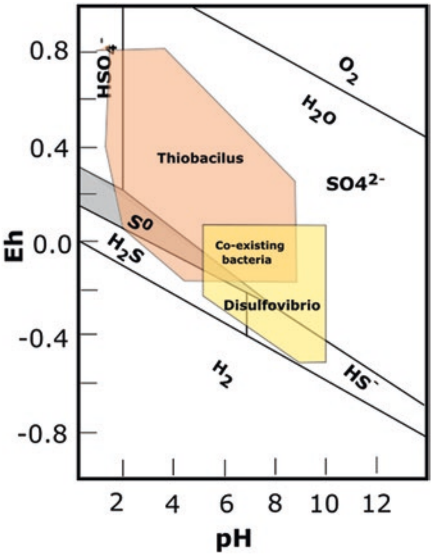


Fig. 15.1 pH-Eh diagram showing stability fields for sulfur compounds at 1 atm and 25 °C. The diagram shows also the activity field for sulfur-oxidizing (*Thiobacillus thioparus*) and sulfate-reducing (*Desulfovibrio desulfuricans*) bacteria

When the pH value is around 9.5, only HS^- will exist. Beyond pH 9.5, S^{2-} start to form, and as pH increases, this anion is the only dominant form. Considering the physiological pH values (7.2–7.4), only 1/3 of sulfur occur as H_2S, although, at skin pH values (4.5–6.5), all sulfur occurs as H_2S. As a rule, at high pH values and high temperatures, H_2S tends to evaporate faster (HSDB 2006). For pH >12, the stable form is S^{2-}, and the H_2S concentration is very small, where there is less therapeutic activity. When the pH value ranges between 7 and 12, HS^- is the dominant species (Forero 2009).

H_2S also depends on the Eh values of the medium, which may be of geological origin or by thermal decomposition of sulfur compounds present in the rocks, where the reaction products are Eh dependent. H_2S production occurs under anoxic conditions where there are the presence of organic matter and the availability of sulfates (National Research Council USA 1979).

Oxidation causes the transformation of H_2S (valence −2) to sulfur (S valence: 0), which is in turn oxidized to hyposulfites ($H_2S_2O_3$: valence +2) and then to sulfites (H_2SO_3: valence +4) and sulfates (H_2SO_4: valence +6). Conversely, reduction leads to the reverse order of formation.

H_2S formation by volcanic activity may be explained by thermal decomposition and/or high-temperature vaporization of sulfides (FeS_2, CuS, NiS, $CuFeS_2$, etc.) (*In*: Mainier and Viola 2005). Hydrogen sulfide occurs around sulfur springs and lakes and is an air contaminant in geothermally active areas. Saline marshes can also produce sulfide. The estimated global release of H_2S from saline marshes into the atmosphere is 8.3×10^5 tonnes per year (Steudler and Peterson 1984).

H_2S occurs naturally in geological formations where the necessary and sufficient components are available for triggering the physicochemical and microbiological mechanisms (Mainier and Rocha 2003; Skrtic 2006). The H_2S-generated volumes by these mechanisms depend on source availability and existing geological conditions (Mainier and Viola 2005).

Sulfur species in a granitic thermal environment can be controlled by deep source gaseous H_2S (Custódio and Llamas Custodio and Llamas 1983) and consequent oxidation or formed from the oxidation of pyrite, in an oxidizing environment, and subsequent reduction of sulfate.

Mineral water as natural groundwater contrasts from other types of groundwater according to the quantity or type of dissolved salts, temperature, and radioactive matter content and is generally classified as therapeutic water used as drinking water or for bathing, inhalation, compresses, etc. (Štambuk-Giljanović 2008).

According to Štambuk-Giljanović (2008), thermomineral water is of atmospheric origin, and after passing through rocks along faults to a depth of 2500–3000 m where it is heated and enriched by minerals, it passes through younger faults, and by ascending drains, it rises to the surface and flows into the secondary aquifer. Thermomineral water used in balneotherapy was a higher mineral content, more than 1000 ppm, and a $T > 20$ °C.

Natural waters containing H_2S concentrations (also named sulfurous mineral waters) are used in medicinal therapeutic baths (WHO 1981).

In 1925 Charles Lepierre (*In*: Acciaiuoli Acciaiouoli 1952) was among the first to use the term sulfur. Since then, this term is used in the chemical classification of this type of mineral water. Sulfurous mineral waters are typically of deep circulation and long residence time, composition, and constant temperature and are bacteriologically pure (Carvalho et al. 1990).

Despite having low mineralization, sulfurous waters have several characteristics, the most striking being the presence of several forms of sulfur (hydrogen sulfide, free sulfide, sulfide groups, polysulfide's acids). Sulfurous waters contain at least 1 ppm of poorly stable forms (H_2S, HS^-, and S^{2-}) or thiosulfate or complex colloidal sulfur and is presented as of simple or mixed sulfide (alkali, carbonated, chlorinated sodium). These waters also contain in varying proportions soluble organic matter, sulfobacterias, and algae that form part of the so-called sulfuraria which gives them certain greasiness to the touch (Cortez 2012). These waters have a characteristic flavor that depends on the remaining mineralized components (Valenzuela 1968).

15.2.1 H_2S: Medicine or Poison?

H_2S has long been considered a highly toxic gas. Its toxicological profile is vast depending on the absorbed amounts (Yu et al. 2014). Our noses can detect H_2S at concentrations of 0.0047 ppm (Guo et al. 2012). At 10 ppm, H_2S leads to eye soreness (Filipovic et al. 2018), and after exposure to 20–100 ppm (air concentration) of H_2S, eye irritation, nausea, airway irritation, and headache may occur (Yu et al. 2014).

H_2S may also cause unconsciousness, collapse, and pulmonary edema when its inhaled concentrations are approximately 500 ppm (Yu et al. 2014). In fact, an exposure to 300–500 ppm represents an imminent threat to life. Above ≥ 500 ppm of

H_2S, hyperpnoea may appear, likely followed by rapid collapse, respiratory disturbance, coma, and till death (Yu et al. 2014; Filipovic et al. 2018).

In most tissues the physiological concentrations of H_2S are in the 4–55 nM range (Benchoam et al. 2019), H_2S above few μM, when in direct contact with cells or tissues, produce effects that are toxic or even lethal in vivo, and a depression in respiratory medullary neurons (leading to a fatal apnea within minutes) and a severe depression in cardiac contractility (leading to a terminal asystole within seconds) can be produced in rodents and in large mammals (Haouzi 2016).

In fact, H_2S is a highly reactive molecule, and its plasma levels return to baseline quickly after systemic administration, presumably due to rapid reaction with plasma proteins and blood-borne cells. Unless lethal levels are used, whenever the amount of H_2S administered, in vivo soluble H_2S concentration barely increases in the blood, remaining in the nM range (Haouzi 2016). How H_2S exerts effects on extrapulmonary systemic organs is yet incompletely defined. Throughout the literature on H_2S, it is reported that the protective and/or therapeutic effects occur in the micromolar range, whereas higher H_2S exposures, i.e., in the millimolar range, potentiate cytotoxicity. H_2S serves as a proverbial "double-edged sword," where it can be extremely beneficial or harmful depending on its concentration and cellular location (Kolluru et al. 2013).

15.2.2 H_2S: Some Biological Effects

The sources of H_2S for the human body are of endogenous origin (enzymatic and non-enzymatic) and/or exogenous. In the context of this work, of particular interest as the external source of H_2S are sulfurous thermal waters (see above).

However, we must remember that absorption of exogenous hydrogen sulfide is performed principally via inhalation and the gas is rapidly absorbed through the lungs (WHO 2003). In a small scale, skin absorption may also occur depending on H_2S concentration and pH (WHO 2003, Gadalla and Snyder 2010). It is unlikely that exogenous H_2S have a direct effect given its short half-life in the organism. Nevertheless, H_2S has pleiotropic effects acting directly and through different signaling mechanisms. It has been suggested that responses are related to the modification of proteins (persulfidation) (Paul and Snyder 2015) that can be further converted to other biochemical forms and participate in multiple biochemical interactions with other molecular targets (Kolluru et al. 2013), interacting with other signaling molecules like nitric oxide and related species (Hosoki et al. 1997), and a third signaling mechanism, metal binding in particular interactions with metalloproteins (Dongó et al. 2018; Kolluru et al. 2013).

It is generally accepted that sulfurous thermal waters have antioxidant, anti-inflammatory, and angiogenesis effects due to the presence of H_2S. The antioxidant properties of H_2S are due to indirect effects. Even under discussion, there is evidence that H_2S induce increase of important intracellular antioxidants and activate other antioxidant mechanisms (Hourihan et al. 2013) by persulfidation (Benchoam et al. 2019) or by formation of internal disulfide bonds (Wakabayashi et al. 2004).

H_2S is normally considered an anti-inflammatory agent. However, it may play dual roles in inflammatory processes, both pro- and anti-inflammatory. At high concentrations, it promotes the generation of pro-inflammatory mediators, whereas in low concentrations, it increases the synthesis of anti-inflammatory mediators (Yu et al. 2014). It is assumed that, considering the typical concentrations of H_2S in sulfurous thermal waters, the anti-inflammatory effects prevail (Wallace et al. 2012).

It is interesting to report that sulfurous thermal waters enhanced the release of IL-10, a potent anti-inflammatory cytokine (Prandelli et al. 2013).

Regarding angiogenesis, it is accepted that H_2S has pro-angiogenic effects enhancing endothelial cell proliferation and migration as was shown in several in vitro studies. It also seems to increase the proliferation and migration of vascular smooth muscle cells (Bir et al. 2012). H_2S has a more dominant role for angiogenesis under hypoxic conditions (Bir et al. 2012).

15.2.3 Use of H_2S Mineral Thermal Waters in Therapy

Sulfurous mineral waters have been traditionally used in medical hydrology as treatment for skin, respiratory, and musculoskeletal disorders (Carbajo and Maraver 2017).

Our focus will be the beneficial health effects of their use. In addition, current knowledge strongly suggest that thermal sulfur waters have additional therapeutic benefits (Carbajo and Maraver 2017), and we will try in subchapter 6 to focus some of the new therapeutic hypotheses without forgetting possible side effects or situations of diseases for which sulfurous thermal waters are contraindicated (Albertini et al. 2008).

15.2.3.1 Myalgia (Muscle Pain)

Balneotherapy with sulfurous water reduces spasticity and pain significantly and can help, namely, in the treatment of post-stroke patients (Erceg-Rukavina and Stefanovski 2015).

The analgesic property of sulfur is confirmed by abundant experimental evidence, but in clinical studies, this agent has been used only in combination with other therapies.

Comparing the therapeutic effect of the sulfur-containing thermal water with that of tap water, it was concluded that the analgesic efficacy and improvement of mobility accomplished using mineral water is significantly superior to that afforded by hydrotherapy with tap water (Balogh et al. 2005).

15.2.3.2 Rheumatic Diseases

Spa therapy represents a popular treatment for many rheumatic diseases, namely, in the following indications: chronic lower back pain, knee osteoarthritis, hand osteoarthritis, fibromyalgia, ankylosing spondylitis, and rheumatoid arthritis (Forestier et al. 2010).

The mechanisms of action of the therapeutic effect of immersion in mineral or thermal water in the treatment of patients with rheumatic diseases are not fully understood. The net benefit is probably the result of a combination of factors, with mechanical, thermal, and chemical effects among the most prominent ones. Buoyancy, immersion, resistance, and temperature all play important roles. According to the gate theory, pain relief may be due to the pressure and temperature of the water on skin; hot stimuli may influence muscle tone and pain intensity, helping to reduce muscle spasm and to increase the pain threshold (Fioravanti et al. 2011; Gálvez et al. 2018) in addition to an anti-inflammatory effect (Gálvez et al. 2018) that in addition to other general effects may delay cartilage destruction (Burguera et al. 2014).

Although sulfur bath therapy is often recommended in mild cases of rheumatoid arthritis, there are still doubts about its efficacy and safety in patients with actively inflamed joints. Therefore, caution is advised in patients with active RA when taking sulfur bath therapy (Kloesch et al. 2012).

Among thermal water treatments, sulfur thermal treatments are largely employed in the management of rheumatic diseases such as OA (Sukenik et al. 1999), and that will be the main topic for the lines below.

Osteoarthritis

Of all rheumatic pathologies, osteoarthritis (OA) is the most commonly treated with balneological interventions (Gálvez et al. 2018).

Being the most popular treatment bath therapies, it should not be forgotten that other approaches like hydropinotherapy have also been reported to give favorable results (Benedetti et al. 2010).

According to the Osteoarthritis Research Society International evidence-based consensus recommendations guiding patients and practitioners, on treatments applicable to all individuals with knee OA, exercise is included (land-based and water-based), and appropriate treatments for specific clinical sub-phenotypes include balneotherapy (McAlindon et al. 2014).

It should be emphasized that there is moderate-quality evidence that aquatic exercise may have small, short-term, and clinically relevant effects on patient-reported pain, disability, in people with knee and hip OA (Bartels et al. 2016) and in combination potentiates balneotherapy treatments in OA patients (Kovács et al. 2016).

For hand osteoarthritis, balneotherapy with sulfurous spa water alone may be effective for the attenuation of pain in patients. The evidence of the potentiating effect of sulfurous water in pain relief comes from a study where patients bathed in sulfurous thermal water were compared with a control group of patients that bathed in running water, evaluating the following parameters: hand pain, joint stiffness and hand grip strength and several evaluation questionnaires health and quality of life.

All the patients experienced a positive effect, however, with longer-lasting improvement in the patients who had bath in the sulfurous spa water, significant even after 3 months in point of pain and quality of life questionnaires (Kovács et al. 2012, 2016).

In a similar study, the same conclusions were achieved for hip osteoarthritis improvement in every parameter under the scope of the study at the end of the treatment, persistency of data after 3 months, and some quality of life maintenance even after 6 months (Kovács et al. 2016), and Forestier et al. (2016) came to the same conclusion regarding knee osteoarthritis. In the case of the hip clinical study, the improvement of joint function was observed, and the decrease of pain was even better with the combination of balneotherapy and home exercise therapy (Kovács et al. 2016).

Comparing the effects of sulfurous water and non-sulfurous water in the treatment of knee osteoarthritis, it was concluded that both of the thermal treatment modalities were found to be effective in the management of the clinical symptoms and quality of life. However, pain and tenderness improved statistically better with balneotherapy (Yurtkuran et al. 2006; Branco et al. 2016).

A clinical trial enrolling 70 patients with generalized osteoarthritis, who received hydrotherapy treatment and crenotherapy with mineral waters (H_2S 34.7–49.6 mg/L) during 15 days (20 min daily) showed that majority of the patients reduced the level of pain in short- and long-term follow-up (1 year). The treatment contributed to the improving of the quality of life in the domain of social relations and environment (Zwolińska et al. 2018).

Other than thermal baths, 12 days of hydropinotherapy thermal treatments to osteoarthritis patients who daily drank 400 mL of sulfurous water (14.5 ppm) result in a decrease of their oxidation, inflammation, and cartilage degradation parameters (Benedetti et al. 2010). Altogether, published results suggest that balneotherapy is a successful treatment of osteoarthritis with a persistent decrease in pain and musculoskeletal function improved, in short to medium term (Kovács et al. 2012, 2016; Forestier et al. 2016).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder, primarily affecting the articular structures and synovial membranes of multiple joints. Sulfur bath therapy has long been used for patients suffering from different rheumatic disorders.

Sukenik et al. (1990) claim that treatments with mud packs alone, sulfur bath alone, or combination of both are effective and safe in reducing objective and subjective indices of rheumatoid arthritis activity for a period of up to 3 months, considering improvement in hand grip, morning stiffness, disease severity, number of active joints, and joint tenderness (Sukenik et al. 1990). It was reported an improvement on quality of life in patients with RA, after treatments for 21 days with sulfur bathing, in addition to the normal pharmacological treatment, as well as daily life activities improvement, suggesting balneotherapy beneficial complementary effects (Santos et al. 2016).

According to a review, updating a Cochrane review of 2008, which evaluated the effects of balneotherapy in patients with RA, there is a low level of evidence showing that balneotherapy is more effective than no treatment at all (Verhagen et al. 2015).

Fibromyalgia

Evaluation of long-term effects of sulfur bathing in fibromyalgia syndrome (FMS) patients showed significantly reduced pains. However, no statistically significant results were found after 3 months of follow-up (Nugraha et al. 2011).

Comparing two groups that stayed for 10 days at a Dead Sea spa, relief in the severity of FM-related symptoms (pain, fatigue, stiffness, and anxiety) and reduced frequency of symptoms (headache, sleep problems, and subjective joint swelling) were reported in both groups but lasted longer in the treatment group (Buskila et al. 2001).

In a systematic review and meta-analysis, regarding the effectiveness of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome, regardless of treatment modality, meta-analysis provided moderate evidence for a medium reduction of pain at the end of treatment and a small reduction of pain for follow-up data. Regardless of the moderate evidence of treatments, authors concluded that more and better-quality studies are needed to confirm the therapeutic benefit of balneotherapy and hydrotherapy (Naumann and Sadaghiani 2014).

15.2.3.3 Respiratory Diseases

Sulfurous mineral water (SMW) inhalations and irrigations have been traditionally used to treat airway diseases (Carbajo and Maraver 2017; Filipovic et al. 2018) in both upper and lower respiratory tract. In treatment of otolaryngological (ORL) diseases (laryngitis, pharyngitis, rhinitis, rhinosinusitis), with thermal SMW inhalations induce amelioration of majority part of the symptoms examined, like cough, nasal itch, and expectoration (Costantino et al. 2003).

Upper Respiratory Tract

Nasal irrigations, in various forms, are a widely used and accepted means of treatment of the symptoms of chronic rhinosinusitis and other sinonasal disease processes and can improve symptoms of sinonasal disease and outcomes (Dunn et al. 2013).

Independent of the potential H_2S effects, nasal irrigations remove static secretions and promote mucociliary clearance evidencing its use (Salami et al. 2010).

Without neglecting the capacity of H_2S absorption by the epithelium of the mucous membranes (more important with inhalation therapy than with nasal irrigations), considering the time and area of contact and the relatively low concentrations in H_2S of the thermal waters, the absorption should be relatively low so that the systemic effects should also be low, being expected to dominate the topical effects.

Comparing the effects of nasal irrigations with sulfurous thermal water with isotonic sodium chloride solution in patients with nonallergic chronic rhinosinusitis, both types of nasal irrigation improved the clinical (endoscopic) and microbiological features of patients with no sign of bacteria, but only sulfurous water irrigations significantly reduced total nasal resistance.

However, small secondary effects such as mild nasal irritation (15% cases) and episodes of extremely limited epistaxis (13% cases) were only reported after sulfurous thermal water irrigations (Ottaviano et al. 2011). Patients with chronic inflammatory upper respiratory tract and middle ear disturbances responsible for onset or persistence of the rhinogenic deafness (such as pharyngitis, rhinitis, laryngitis, chronic catarrhalis otitis, and chronic rhinosinusitis inflammation) when submitted to sulfur thermal water inhalatory therapy with humid-hot vapor plus thermal Politzer inhalation, shows improvement not just in most symptoms but also in the middle ear function (Costantino et al. 2006).

In the treatment of the recurrent upper respiratory tract disturbances, the treatment using sulfurous thermal water inhalations reduces significantly the frequency, duration, severity, and social impact in children with RURT infections (Salami et al. 2008; Varricchio et al. 2013). Current knowledge indicates that sulfur thermal water applications can be recommended as additional nonpharmacological treatment in upper airway diseases (Keller et al. 2014).

Lower Respiratory Tract

In the lower respiratory system, H_2S has potential therapeutic uses against fibrosis and chronic obstructive pulmonary disease (COPD) (Fang et al. 2009). Absorption of H_2S through the lungs is almost immediate, and it is necessary to remember that inhalation treatments with sulfurous thermal waters may present local and systemic effects.

Locally, it is known that H_2S induces bronchodilation and relaxation of tracheal smooth muscle cells on a mouse model, probably by activating the calcium-activated potassium channel (Huang et al. 2014).

Regarding COPD, it is considered that the inhalation of sulfurous mineral waters improves the health state of patients (Carbajo and Maraver 2017; Filipovic et al. 2018). A significant improvement in the COPD assessment test (CAT) questionnaire was shown 1 month after the end of the 12-day inhalatory treatment only in patients receiving sulfurous water compared with isotonic saline inhalation demonstrating an improvement in health status in COPD patients (Contoli et al. 2013). It should be noted that an epidemiological study with a cohort of 33,804 subjects aimed to investigate the association between chronic low-level exposure to H_2S and health outcomes reported risk increases associated respiratory diseases in particular COPD (Nuvolone et al. 2019).

Although respiratory symptoms are the most consistently reported symptoms in similar studies, there is no consistent evidence of pulmonary function deficit among those chronically exposed to low H_2S concentrations (Lewis and Copley 2015). There is no evidence that non-sulfurous thermal water inhalation treatments may bring some advantages to COPD patients (Pellegrini et al. 2005; Guarnieri et al. 2010).

H_2S treatment may diminish pulmonary fibrosis. H_2S treatment suppressed the migration, proliferation, and myofibroblast transdifferentiation of a human lung fibroblast cell line (Perry et al. 2011). No reports were found regarding pulmonary fibrosis and sulfurous thermal water effects.

15.2.3.4 Dermatological/Skin Diseases

Skin Absorption of H_2S

Absorption of salts through the skin is limited. However, as H_2S is a gas, it is able to penetrate the skin and mucosae and can therefore, through this absorption ion route, act at the cell level both in the skin and in internal organs of the organism. Moreover, skin adsorption of H_2S is favored by the skin low pH (<6). It should be also considered that H_2S will be more easily absorbed through the skin and mucosa than its soluble salts (HS^- and S^{2-}) (Paul and Snyder 2015). Overall, this means that H_2S molecules will more actively penetrate the skin rather than remaining on the surface (Paul and Snyder 2015).

Therapeutic Uses of Sulfurous Thermal Waters in Dermatology

Since sulfur, in its varied number of chemical species, can penetrate the skin, sulfur-rich balneotherapy has been suggested to be effective in the treatment of several dermatological diseases where psoriasis and psoriatic arthritis (Halevy and Sukenik 1998), contact dermatitis, and atopic dermatitis (Carbajo and Maraver 2017) deserve to be highlighted. It has been claimed that on skin, sulfurous mineral water may cause vasodilation, analgesia, immune response inhibition, keratolytic effects, and anti-inflammatory and antipruritic effects (Matz et al. 2003). Also, it has bactericidal and antifungal properties which have determined its use for the treatment of infected leg ulcers, tinea versicolor, tinea corporis, and tinea capitis (Carbajo and Maraver 2017).

In vivo experiments with concentrations higher than 2 mM of NaHS on the treatment of psoriatic lesions confirm in vitro results (Gobbi et al. 2009). Regarding actual knowledge, a sulfur-rich balneotherapy may be effective in the treatment of psoriasis. However, their use can be counterproductive on thermal waters with low levels of H_2S since it may promote keratinocyte proliferation (Jin et al. 2015).

15.2.3.5 Wound Healing

Coming from the Roman times, thermal waters are used to wound heal treatments. A central aspect of wound healing properties of H_2S, by direct contact or absorbed through the skin, is the potential pro-angiogenic effect and new microvessel formation (Carbajo and Maraver 2017).

Wound treatments with thermal waters with low levels of H_2S may be advantageous (most of the sulfur balnearies have low levels of H_2S). In general, topical application of sulfurous mineral waters in well-ventilated and controlled environments, such as spas, can be considered safe, nevertheless not free of complications. It seems that sulfurous mineral waters are anti-irritants for the majority of users (Ferreira et al. 2010) but there are reports of dermatitis on sulfurous thermal water users (Sun and Sue 1995; Lee and Wu 2014), in one case with lesions consistent with coagulation necrosis of the epidermis and papillary dermis and neutrophil infiltration, typical of a superficial second-degree burn (Lee and Wu 2014).

Note: due to the particular interest of the treatment of integumentary wounds in the diabetic patient, this subject will be referred again in the section Diabetes.

15.2.3.6 Other Diseases and H_2S

Cancer and H_2S

The roles of H_2S in cancer development and progression are still controversial. Relevant to cancer biology include stimulation of angiogenesis, regulation of intracellular signaling and cell death, and cellular bioenergetics (Hellmich and Szabo 2015). Clearly the effects of H_2S strongly depend on its concentration with a relatively narrow safety window. However, it is not clear which levels of H_2S concentration promote cell proliferation. Considering experiments with several different cancer cell lines, even relatively high doses of NaHS markedly promoted cell proliferation (Zhen et al. 2015).

Overall, literature suggest that H_2S is a pro-proliferative factor in human cancer cells partly by accelerating the progression of the cell cycle (Sen 2017). Interesting is the fact that at concentrations near to toxic levels H_2S-donating drugs have great potential as anti-cancer agents (Kashfi 2014; Chan and Wong 2017).

In the face of the actual knowledge, the effects of H_2S on cancer are complicated and still unclear. Interestingly, on an epidemiological study considering the chronic low-level exposure to H_2S and health outcomes, neoplasms were negatively associated with increased H_2S exposure (Nuvolone et al. 2019).

15.2.3.7 Diabetes and Diabetes Complications

Wound Healing in Diabetic Patients

One of the most common complications of diabetes is late wound healing usually associated with microvascular changes and keratinocyte dysfunction.

The use of sulfurous thermal waters baths in the treatment of wounds in diabetics can be beneficial. There are some evidences that indicate that H_2S improves diabetic wound healing by several mechanisms such as protecting endothelial cells against apoptosis induced by type 2 diabetes by suppressing excessive autophagy (Liu et al. 2016) and stimulating angiogenesis (Sen 2017) or protecting human skin keratinocytes from methylglyoxal-induced injury and dysfunction (methylglyoxal is a collagen Maillard reaction product elevated in diabetic skin tissue and plasma) (Yang et al. 2014).

Diabetes and Cardiovascular Complications

In animal models, it has been demonstrated that vascular reactivity, plasma H_2S levels, and vascular H_2S production all decline progressively as the severity of diabetes increases over time (Brancaleone et al. 2008). In patients with type 2 diabetes, blood H_2S levels are significantly lower which paralleled poor glycemic control (Jain et al. 2010), and in type 1 diabetic patients, the reduction in CSE expression and activity was shown in peripheral blood mononuclear cells (Manna et al. 2014). Furthermore, a reduction in the plasma H_2S levels was found to be related to a history of cardiovascular diseases in patients with type 2 diabetes (Suzuki et al. 2017).

Recent studies provide evidence that H_2S counteracts the hyperglycemic effect (Manna and Jain 2013; Sen 2017) and protects cardiomyocytes (H9c2 cardiac cells) against high glucose-induced inflammation and injury, including cytotoxicity, apoptosis, overproduction of ROS, and the dissipation of MMP (Yang et al. 2007; Xu et al. 2015; Liang et al. 2016).

Among other possible cardioprotective effects for the population in general but particularly important for diabetes patients, sulfurous mineral water prevents the development of fibrosis in the heart (El-Seweidy et al. 2011) probably by attenuation of autophagy (Xiao et al. 2015).

Diabetes Renal Complications

H_2S appears to play an important role in the onset and progression of renal diabetes complications since plasma H_2S levels are lower in patients with diabetic undergoing chronic hemodialysis (Li et al. 2014). Overall, the reduction of endogenous H_2S contribute to diabetic injury, and the supply of exogenous H_2S protects tissues from diabetic injury through anti-apoptosis, anti-fibrosis, inhibited oxidative stress, and inflammation in different complications, including cardiomyopathy, vascular injury, retinopathy, nephropathy, and encephalopathy (Qian et al. 2018).

Sulfurous water counteracted the development and ameliorate diabetic nephropathy in diabetic rats with impaired kidney function reflected on improved renal performance (Safar and Abdelsalam 2015).

Sulfurous Thermal Water Treatments and Diabetes

It is claimed that there are beneficial effects of drinking sulfurous water on diabetes and long-term diabetes-associated complications (El-Seweidy et al. 2011; Safar and Abdelsalam 2015). However, the benefits of H_2S in diabetics are still controversial, namely, since even at H_2S physiologically concentrations, it may induce apoptosis of insulin-secreting beta cells (Yang et al. 2007).

15.2.3.8 H_2S and the Nervous System

In the nervous system, H_2S is considered to be a neuromodulator (Benchoam et al. 2019). Several neurological diseases have been associated with low levels of H_2S, and it was reported that H_2S production is markedly decreased in Huntington's disease (Paul et al. 2014), Parkinson's disease (Vandiver et al. 2013), or Alzheimer's disease patients as compared to healthy individuals (Eto et al. 2002).

Concerning Alzheimer's disease, H_2S induced a decrease in amyloid beta (Aβ) release (the main component of amyloid plaques) (Nagpure and Bian 2014). Regarding Parkinson's disease (PD), current knowledge indicates that H_2S may function as an effective neuromodulator to regulate striatal neurotransmission and enhanced parkin activity (preventing dopaminergic cell death) (Vandiver et al. 2013). Using an animal PD experimental model, the H_2S inhalation of 40 ppm for 8 h a day for 7 days prevent neurodegeneration and movement disorder (Kida et al. 2010).

Moreover, H_2S exerts neuroprotection against hypoxia-induced neurotoxicity through its anti-inflammatory effect in microglia (Sen 2017). It is also possible that H_2S own protective effects in cerebral ischemia/reperfusion (I/R) injury due to anti-apoptotic properties (Marutani et al. 2015) and of parkin activation (Vandiver et al. 2013).

15.2.3.9 Renal System

In the renal system, increased levels of H_2S suppress isoproterenol-induced renin release (Lu et al. 2012). However, the underlying mechanism by which H_2S regulates renin release is unclear (Filipovic et al. 2018). The usefulness of sulfurous thermal waters for therapy in disorders of the renal system seems of small impact.

15.2.3.10 Cardiovascular Diseases

In vitro, ex vivo, and in vivo studies clearly show that exogenous and endogenous H_2S have cardioprotective properties (Nicholson and Calvert 2010), mostly vasculoprotective effects (Pan et al. 2011).

Mechanisms of Vasodilatation and Antihypertensive Effects of H_2S

Endogenous H_2S plays a pivotal role in the basal regulation of vessel tone. Similarly, some studies demonstrating that exogenous H_2S lowers systolic blood pressure through vasodilation have been reported since the 1960s for H_2S baths (Filipovic et al. 2018). In the cardiovascular system, H_2S can cause smooth muscle relaxation by inducing the opening of potassium channels among other proposed mechanisms (Tang et al. 2005; Cuevasanta et al. 2017). Furthermore, glibenclamide, a selective potassium ATP channel (KATP) blocker, partially inhibits the vasodilatory effects of H_2S (Papapetropoulos et al. 2009). There are also little thoughts that NO and H_2S interact in a coordinate fashion in regulating vascular tone (Hosoki et al. 1997).

H_2S, in many respects, is now viewed as an enhancer of eNOS-mediated vasorelaxant, angiogenic, and cardioprotective responses (Sellak et al. 2013). Moreover, regulation of blood pressure by hydrogen sulfide or by its donors might occur directly on the vascular wall and/or indirectly with the alteration of the renin-angiotensin system (Dongó et al. 2018). In this regard, it has been found that H_2S inhibit renin and angiotensin-converting enzyme (ACE) activities in rat models of renovascular hypertension and human endothelial cells (Yu et al. 2014).

Consistent with the above findings, diminished H_2S levels are associated with constriction of blood vessels, thus increasing blood pressure (Yang et al. 2008). Interestingly, however, higher doses of NaHS caused a biphasic relaxation/constriction response, a response that warrants further investigation (Cheng et al. 2004).

Not forgetting that several studies have shown that H_2S causes both contraction and relaxation of isolated vessels, depending on the concentrations of H_2S administered (Yu et al. 2014), directly related with its potential vasodilator properties, one of the main effects attributed to the administration of exogenous H_2S is their antihypertensive effect.

Atherosclerosis

It was shown (Mani et al. 2013) that decreased endogenous H_2S production by CSE (the primary H_2S-producing enzyme in the vasculature) accelerates atherosclerosis in mice and that H_2S supplementation by exogenous H_2S donors attenuates (Bhatia 2015).

Hypertension and hyperhomocysteinemia represent two major risk factors of atherosclerotic cardiovascular diseases. In this aspect, H_2S significantly lowers blood pressure as well as reduces plasma homocysteine levels in experimental animals (Xu et al. 2014). Moreover, inhibition of inflammation by H_2S contributes to its antiatherosclerotic effect (Yu et al. 2014). Recent studies showed H_2S is protective against hypertriglyceridemia (HTG) and nonalcoholic fatty liver disease (NAFLD), while the mechanism remains to be explored (Sun et al. 2015).

It is possible that balneotherapy may have some effect on atherosclerosis since a standard hydroponic treatment (500 ml per day for 2 weeks) results in a significant decrease in both lipid and protein oxidation products in plasma samples obtained from healthy volunteers subjected to a cycle of hydroponic therapy with sulfurous mineral water (14.5 ppm) (Benedetti et al. 2009).

Cardioprotective Effects in Myocardial Infarction and Ischemia/Reperfusion (MI and I/R)

There is much evidence to suggest that H_2S also protects against injury via anti-apoptotic signaling during myocardial ischemia/reperfusion (IR) (Nicholson and Calvert 2010; Wang et al. 2011; Sen 2017; Wetzel and Wenke 2019). Other possible pro-survival roles of H_2S are the result of reducing inflammation (Wetzel and Wenke 2019), angiogenesis stimulation (namely, by increasing the expression of VEGF) (Qipshidze et al. 2012) reducing free radical-induced stress, promoting mitochondrial function, activating vascularization pathways (Wetzel and Wenke 2019), and preventing Ca^{2+} overload in ischemic heart (Hu et al. 2008, 2011).

Taken together, H_2S has been shown to be cytoprotective in multiple organ systems (Kolluru et al. 2013). It protects the heart during I/R injury, both in pre- and post-conditioning (Kolluru et al. 2013; Sen 2017), through decreasing myocardial damage, infarct size, and apoptosis, improving cardiac function, and increasing cell viability and autophagy in the aged hearts and cardiomyocytes (Li et al. 2015). Whether it is endogenous or exogenous, H_2S has a wide range of protective functions after I/R injury throughout the body (Nicholson and Calvert 2010).

Thermal Waters and the Cardiovascular System

Probably the most exciting evidence relates to hypertensive patients who had lowered blood H_2S levels compared to healthy controls. Sulfide-containing baths are fairly world widespread, and the claimed effects do involve decreased blood pressure and were reported to be effective in treating hypertensive patients (Dongó et al. 2018).

Mancini et al. (2003) described additional benefits of thermal hydrotherapy (balneokinesis) with sulfurous water in patients with symptomatic varices who submitted to elastic compression. According to these authors, the improvement in the venoarteriolar reflex observed could support these subjective benefits. In another study, a randomized trial comparing balneohydrotherapy versus waiting list patients concluded that balneohydrotherapy seems to improve the quality of life of patients with chronic venous insufficiency (Forestier 2014).

Therapy with sulfurous water can provide beneficial effects in modification of the lipoprotein's metabolism caused by hypercholesterolemia suggesting its anticholesterolemic use. Rats subjected to a hypercholesterolemic diet with sulfurous thermal water had a less increased cholesterol plasma level, an increased level of HDL cholesterol, and a stabilized level of cholesterol LDL compared to controls (Toussaint et al. 1986).

With the current state of the art regarding the cardiovascular effects of H_2S, we can suggest that this is an area still little explored in the use of sulfurous thermal waters.

Other Vascular Effects

Since H_2S is considered vasodilator and given its convergent mechanism with NO, it was suggested that sulfurous thermal waters are potentially useful for the treatment of erectile dysfunction (Bełtowski 2015). However, no experimental works or reports were found in the literature regarding the use of sulfurous thermal waters (or other) for this purpose.

References

Acciaiouoli LMC (1952) Le Portugal Hydromineral. Lisbonne, IV, 248 pp

Albertini MC, Teodori L, Accorsi A, Soukri A, Campanella L, Baldoni F, Dachà M (2008) Sulphurous mineral water oral therapy: effects on erythrocyte metabolism. Food Chem Toxicol 46(10):3343–3350. https://doi.org/10.1016/j.fct.2008.08.008. Epub 2008 Aug 22

Balogh Z, Ordögh J, Gász A, Német L, Bender T (2005) Effectiveness of balneotherapy in chronic low back pain – a randomized single-blind controlled follow-up study. Forsch Komplementarmed Klass Naturheilkd 12(4):196–201. Epub 2005 Aug 29

Bartels EM, Juhl CB, Christensen R, Hagen KB, Danneskiold-Samsøe B, Dagfinrud H, Lund H (2016) Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev 3, CD005523. https://doi.org/10.1002/14651858.CD005523.pub3. Review

Bełtowski J (2015) Hydrogen sulphide in pharmacology and medicine – an update. Pharmacol Rep 67(3):647–658. https://doi.org/10.1016/j.pharep.2015.01.005. Epub 2015 Jan 22

Benchoam D, Cuevasanta E, Möller MN, Alvarez B (2019) Hydrogen sulphide and persulphides oxidation by biologically relevant oxidizing species. Antioxidants (Basel) 8(2):pii: E48. https://doi.org/10.3390/antiox8020048

Benedetti S, Benvenuti F, Nappi G et al (2009) Antioxidative effects of sulphurous mineral water: protection against lipid and protein oxidation. Eur J Clin Nutr 63:106–112

Benedetti S, Canino C, Tonti G, Medda V, Calcaterra P, Nappi G, Salaffi F, Canestrari F (2010) Biomarkers of oxidation, inflammation and cartilage degradation in osteoarthritis patients undergoing sulphur-based spa therapies. Clin Biochem 43(12):973–978. https://doi.org/10.1016/j.clinbiochem.2010.05.004. Epub 2010 May 20

Bhatia M (2015) H2S and inflammation: an overview. Handb Exp Pharmacol 230:165–180. https://doi.org/10.1007/978-3-319-18144-8_8. Review

Bir SC, Kolluru GK, McCarthy P, Shen X, Pardue S, Pattillo CB, Kevil CG (2012) Hydrogen sulphide stimulates ischemic vascular remodeling through nitric oxide synthase and nitrite reduction activity regulating hypoxia-inducible factor-1α and vascular endothelial growth factor-dependent angiogenesis. J Am Heart Assoc 1(5):e004093. https://doi.org/10.1161/JAHA.112.004093. Epub 2012 Oct 25

Brancaleone V, Roviezzo F, Vellecco V, De Gruttola L, Bucci M, Cirino G (2008) Biosynthesis of H2S is impaired in non-obese diabetic (NOD) mice. Br J Pharmacol 155(5):673–680. https://doi.org/10.1038/bjp.2008.296. Epub 2008 July 21

Branco M, Rêgo NN, Silva PH, Archanjo IE, Ribeiro MC, Trevisani VF (2016) Bath thermal waters in the treatment of knee osteoarthritis: a randomized controlled clinical trial. Eur J Phys Rehabil Med 52(4):422–430. Epub 2016 Feb 19

Burguera EF, Vela-Anero A, Magalhães J, Meijide-Faílde R, Blanco FJ (2014) Effect of hydrogen sulphide sources on inflammation and catabolic markers on interleukin 1β-stimulated human articular chondrocytes. Osteoarthr Cartil 22(7):1026–1035. https://doi.org/10.1016/j.joca.2014.04.031. Epub 2014 May 14

Buskila D, Abu-Shakra M, Neumann L, Odes L, Shneider E, Flusser D, Sukenik S (2001) Balneotherapy for fibromyalgia at the Dead Sea. Rheumatol Int 20(3):105–108

Carbajo JM, Maraver F (2017) Sulphurous mineral waters: new applications for health. Evid Based Complement Alternat Med 2017:8034084. https://doi.org/10.1155/2017/8034084. Epub 2017 Apr 6

Carvalho MR, Cruz JV, Almeida C, Silva MO (1990) Hidrogeoquímica das águas dos granitos hercínicos das Beiras. In Geolis, Rev. da Sec. de Geol. Ec. e Aplic. 1990, IV (1,2), 229–248

Chan SJ, Wong PT (2017) Reprint of: hydrogen sulphide in stroke: protective or deleterious? Neurochem Int 107:78–87. https://doi.org/10.1016/j.neuint.2016.11.016

Cheng Y, Ndisang JF, Tang G, Cao K, Wang (2004) Hydrogen sulphide-induced relaxation of resistance mesenteric artery beds of rats. Am J Physiol Heart Circ Physiol 287(5):H2316–H2323. Epub 2004 Jun 10

Contoli M, Gnesini G, Forini G, Marku B, Pauletti A, Padovani A, Casolari P, Taurino L, Ferraro A, Chicca M, Ciaccia A, Papi A, Pinamonti S (2013) Reducing agents decrease the oxidative burst and improve clinical outcomes in COPD patients: a randomised controlled trial on the effects of sulphurous thermal water inhalation. Sci World J 2013:927835. https://doi.org/10.1155/2013/927835. eCollection 2013

Cortez JA (2012) Águas Minerais Naturais e de Nascente da Região Centro. Mare Liberum – Editora 2012, FEDRAVE

Costantino M, Lampa E, Nappi G (2006) Effectiveness of sulphur spa therapy with politzer in the treatment of rhinogenic deafness. Acta Otorhinolaryngol Ital 26(1):7–13

Costantino M, Rossi F, Lampa E (2003) Inhalation therapy with sulphur water in ORL: clinical-experimental study. Clin Ter 154(6):395–400

Cuevasanta E, Möller MN, Alvarez B (2017) Biological chemistry of hydrogen sulphide and persulphides. Arch Biochem Biophys 617:9–25. https://doi.org/10.1016/j.abb.2016.09.018. Epub 2016 Sep 30

Custodio E, Llamas MR (1983) Hidrogeología Subterránea. Vol I e II, 2ª Edição. 1983. Ed. Omega, Barcelona, 2350 pp

Dongó E, Beliczai-Marosi G, Dybvig AS, Kiss L (2018) The mechanism of action and role of hydrogen sulphide in the control of vascular tone. Nitric Oxide 81:75–87. https://doi.org/10.1016/j.niox.2017.10.010. Epub 2017 Oct 31. Review

Dunn JD, Dion GR, KC MM (2013) Efficacy of nasal irrigations and nebulizations for nasal symptom relief. Curr Opin Otolaryngol Head Neck Surg 21(3):248–251. https://doi.org/10.1097/MOO.0b013e32835f80bb

El-Seweidy MM, Sadik NA, Shaker OG (2011) Role of sulphurous mineral water and sodium hydrosulphide as potent inhibitors of fibrosis in the heart of diabetic rats. Arch Biochem Biophys 506(1):48–57. https://doi.org/10.1016/j.abb.2010.10.014. Epub 2010 Oct 20

Erceg-Rukavina T, Stefanovski M (2015) Balneotherapy in treatment of spastic upper limb after stroke. Med Arch 69(1):31–33. https://doi.org/10.5455/medarh.2015.69.31-33. Epub 2015 Feb 21

Eto K, Asada T, Arima K, Makifuchi T, Kimura H (2002) Brain hydrogen sulphide is severely decreased in Alzheimer's disease. Biochem Biophys Res Commun 293(5):1485–1488

Fang L, Li H, Tang C, Geng B, Qi Y, Liu X (2009) Hydrogen sulphide attenuates the pathogenesis of pulmonary fibrosis induced by bleomycin in rats. Can J Physiol Pharmacol 87(7):531–538. https://doi.org/10.1139/y09-039

Ferreira MO, Costa PC, Bahia MF (2010) Effect of São Pedro do Sul thermal water on skin irritation. Int J Cosmet Sci 32(3):205–210. https://doi.org/10.1111/j.1468-2494.2010.00527.x

Filipovic MR, Zivanovic J, Alvarez B, Banerjee R (2018) Chemical biology of H2S signaling through persulfidation. Chem Rev 118(3):1253–1337. https://doi.org/10.1021/acs.chemrev.7b00205. Epub 2017 Nov 7

Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M (2011) Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int 31(1):1–8. https://doi.org/10.1007/s00296-010-1628-6. Epub 2010 Dec 1

Forero BA (2009) Avaliação da Resistência à Corrosão sob Tensão e Suscetibilidade à Fragilização por Hidrogênio de Juntas Soldadas Circunferenciais de Aço API X-80. Rio de Janeiro: Pontifícia Universidade Católica

Forestier R (2000) Magnitude and duration of the effects of two spa therapy courses on knee and hip osteoarthritis: an open prospective study in 51 consecutive patients. Joint Bone Spine 67(4):296–304

Forestier R, Desfour H, Tessier J-M, Françon A, Foote A, Genty C, Rolland C, Roques C-F, Bosson J-L (2010) Spa therapy in the treatment of knee osteoarthritis: a large randomized multicentre trial. Ann Rheum Dis 69:660–665

Forestier R, Erol FB (2014) Is (creno) balneotherapy a drug, a surgical procedure or a non-pharmacological treatment? E-Letter on EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 73(2):e6. http://dx.doi.org/10.1136/annrheumdis-2013-204787

Forestier R, Erol Forestier FB, Francon A (2016) Spa therapy and knee osteoarthritis: a systematic review. Ann Phys Rehabil Med 59(3):216–226. https://doi.org/10.1016/j.rehab.2016.01.010. Epub 2016 Mar 17

Gadalla MM, Snyder SH (2010) Hydrogen sulphide as a gasotransmitter. J Neurochem 113(1):14–26. https://doi.org/10.1111/j.1471-4159.2010.06580.x. Epub 2010 Jan 12. Review

Gálvez I, Torres-Piles S, Ortega-Rincón E (2018) Balneotherapy, immune system, and stress response: a hormetic strategy? Int J Mol Sci 19(6):pii: E1687. https://doi.org/10.3390/ijms19061687

Gobbi G, Ricci F, Malinverno C, Carubbi C, Pambianco M, Gd P, Vitale M, Mirandola P (2009) Hydrogen sulphide impairs keratinocyte cell growth and adhesion inhibiting mitogen-activated protein kinase signaling. Lab Investig 89(9):994–1006. https://doi.org/10.1038/labinvest.2009.61. Epub 2009 Jun 22

Guarnieri G, Ferrazzoni S, Scarpa MC, Lalli A, Maestrelli P (2010) Effects of inhalation of thermal water on exhaled breath condensate in chronic obstructive pulmonary disease. Respiration 79(3):216–221. https://doi.org/10.1159/000227801. Epub 2009 July 3

Guo W, Kan JT, Cheng ZY, Chen JF, Shen YQ, Xu J, Wu D, Zhu YZ (2012) Hydrogen sulphide as an endogenous modulator in mitochondria and mitochondria dysfunction. Oxidative Med Cell Longev 2012:878052. https://doi.org/10.1155/2012/878052. Epub 2012 Dec 5

Halevy S, Sukenik S (1998) Different modalities of spa therapy for skin diseases at the Dead Sea area. Arch Dermatol 134(11):1416–1420

Haouzi P (2016) Is exogenous hydrogen sulphide a relevant tool to address physiological questions on hydrogen sulphide? Respir PhysiolNeurobiol 229:5–10. https://doi.org/10.1016/j.resp.2016.03.015. Epub 2016 Mar 30

Hellmich MR, Szabo C (2015) Hydrogen Sulphide and Cancer. Handb Exp Pharmacol 230:233–241. https://doi.org/10.1007/978-3-319-18144-8_12. Review

Hosoki R, Matsuki N, Kimura H (1997) The possible role of hydrogen sulphide as an endogenous smooth muscle relaxant in synergy with nitric oxide. Biochem Biophys Res Commun 237(3):527–531

Hourihan JM, Kenna JG, Hayes JD (2013) The gasotransmitter hydrogen sulphide induces nrf2-target genes by inactivating the keap1 ubiquitin ligase substrate adaptor through formation of a disulphide bond between cys-226 and cys-613. Antioxid Redox Signal 19(5):465–481. https://doi.org/10.1089/ars.2012.4944. Epub 2013 Jan 16

HSDB (2006) Hydrogen sulfide: environmental standards & regulations. Hazardous Substances Databank National Library of Medicine, Bethesda. http://toxnetnlmnihgov/cgibin/sis/htmlgen?HSDB June 12, 2006

Hu Y, Chen X, Pan TT, Neo KL, Lee SW, Khin ES, Moore PK, Bian JS (2008) Cardioprotection induced by hydrogen sulphide preconditioning involves activation of ERK and PI3K/Akt pathways. Pflugers Arch 455(4):607–616. Epub 2007 Aug 1

Hu LF, Li Y, Neo KL, Yong QC, Lee SW, Tan BK, Bian JS (2011) Hydrogen sulphide regulates Na+/H+ exchanger activity via stimulation of phosphoinositide 3-kinase/Akt and protein kinase G pathways. J Pharmacol Exp Ther 39(2):726–735. https://doi.org/10.1124/jpet.111.184754. Epub 2011 Aug 24

Huang J, Luo YL, Hao Y, Zhang YL, Chen PX, Xu JW, Chen MH, Luo YF, Zhong NS, Xu J, Zhou WL (2014) Cellular mechanism underlying hydrogen sulphide induced mouse tracheal smooth muscle relaxation: role of BKCa. Eur J Pharmacol 741:55–63. https://doi.org/10.1016/j.ejphar.2014.07.004. Epub 2014 July 14

Jain SK, Bull R, Rains JL, Bass PF, Levine SN, Reddy S, McVie R, Bocchini JA (2010) Low levels of hydrogen sulphide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? Antioxid Redox Signal 12(11):1333–1337. https://doi.org/10.1089/ars.2009.2956

Jin Z, Chan H, Ning J, Lu K, Ma D (2015) The role of hydrogen sulphide in pathologies of the vital organs and its clinical application. J Physiol Pharmacol 66(2):169–179

Kashfi K (2014) Anti-cancer activity of new designer hydrogen sulphide-donating hybrids. Antioxid Redox Signal 20(5):831–846. https://doi.org/10.1089/ars.2013.5308. Epub 2013 Jun 7

Keller S, König V, Mösges R (2014) Thermal water applications in the treatment of upper respiratory tract diseases: a systematic review and meta-analysis. J Allergy (Cairo) 2014:943824. https://doi.org/10.1155/2014/943824. Epub 2014 Jun 1

Kida K, Yamada M, Tokuda K, Marutani E, Kakinohana M, Kaneki M et al (2010) Inhaled hydrogen sulphide prevents neurodegeneration and movement disorder in a mouse model of Parkinson's disease. Antioxid Redox Signal 15:343–352

Kloesch B, Liszt M, Krehan D, Broell J, Kiener H, Steiner G (2012) High concentrations of hydrogen sulphide elevate the expression of a series of pro-inflammatory genes in fibroblast-like synoviocytes derived from rheumatoid and osteoarthritis patients. Immunol Lett 141(2):197–203. https://doi.org/10.1016/j.imlet.2011.10.004. Epub 2011 Oct 12

Kolluru GK, Shen X, Bir SC, Kevil CG (2013) Hydrogen sulphide chemical biology: pathophysiological roles and detection. Nitric Oxide 35:5–20. https://doi.org/10.1016/j.niox.2013.07.002. Epub 2013 July 9

Kovács C, Pecze M, Tihanyi Á, Kovács L, Balogh S, Bender T (2012) The effect of sulphurous water in patients with osteoarthritis of hand. Double-blind, randomized, controlled follow-up study. Clin Rheumatol 31(10):1437–1442. https://doi.org/10.1007/s10067-012-2026-0. Epub 2012 July 29

Kovács C, Bozsik Á, Pecze M, Borbély I, Fogarasi A, Kovács L, Tefner IK, Bender T (2016) Effects of Sulphur bath on hip osteoarthritis: a randomized, controlled, single-blind, follow-up trial: a pilot study. Int J Biometeorol 60(11):1675–1680. Epub 2016 Jun 21

Lee CC, Wu YH (2014) Sulphur spring dermatitis. Cutis 94(5):223–225

Lewis RJ, Copley GB (2015) Chronic low-level hydrogen sulphide exposure and potential effects on human health: a review of the epidemiological evidence. Crit Rev Toxicol 45(2):93–123. https://doi.org/10.3109/10408444.2014.971943. Epub 2014 Nov 28

Li H, Feng SJ, Zhang GZ, Wang SX (2014) Correlation of lower concentrations of hydrogen sulphide with atherosclerosis in chronic hemodialysis patients with diabetic nephropathy. Blood Purif 38(3–4):188–194. https://doi.org/10.1159/000368883. Epub 2014 Dec 16

Li H, Wang Y, Wei C, Bai S, Zhao Y, Li H, Wu B, Wang R, Wu L, Xu C (2015) Mediation of exogenous hydrogen sulphide in recovery of ischemic post-conditioning-induced cardioprotection via down-regulating oxidative stress and up-regulating PI3K/Akt/GSK-3β pathway in isolated aging rat hearts. Cell Biosci 5:11. https://doi.org/10.1186/s13578-015-0003-4. eCollection 2015

Liang W, Chen J, Mo L, Ke X, Zhang W, Zheng D, Pan W, Wu S, Feng J, Song M, Liao X (2016) ATP-sensitive K^+ channels contribute to the protective effects of exogenous hydrogen sulphide against high glucose-induced injury in H9c2 cardiac cells. Int J Mol Med 37(3):763–772. https://doi.org/10.3892/ijmm.2016.2467. Epub 2016 Jan 25

Lima A (2011) Origens do Fluido e da Mineralização das Águas Sulfúreas. Universidade do Minho 2011:29–48

Liu J, Wu J, Sun A, Sun Y, Yu X, Liu N, Dong S, Yang F, Zhang L, Zhong X, Xu C, Lu F, Zhang W (2016) Hydrogen sulphide decreases high glucose/palmitate-induced autophagy in endothelial cells by the Nrf2-ROS-AMPK signaling pathway. Cell Biosci 6:33. https://doi.org/10.1186/s13578-016-0099-1. eCollection 2016

Lu M, Liu YH, Ho CY, Tiong CX, Bian JS (2012) Hydrogen sulphide regulates cAMP homeostasis and renin degranulation in As4.1 and rat renin-rich kidney cells. Am J Physiol Cell Physiol 302(1):C59–C66. https://doi.org/10.1152/ajpcell.00341.2010. Epub 2011 Sep 21

Mainier FB, Rocha ADA (2003) H_2S: Novas Rotas de Remoção Química e Recuperação de Enxofre. 2° Congresso Brasileiro de P&D em Petróleo e Gás. 2003. Rio de Janeiro

Mainier FB, Viola EDM (2005) O Sulfeto De Hidrogénio (H2S) e o Meio Ambiente, Universidade Federal Fluminense, INMETRO/LATEC (UFF). II Simpósio de Excelência em Gestão e Tecnologia – SEGeT. 2005

Mancini S Jr, Piccinetti A, Nappi G, Mancini S, Caniato A, Coccheri S (2003) Clinical, functional and quality of life changes after balneokinesis with sulphurous water in patients with varicose veins. Vasa 32(1):26–30

Mani S, Li H, Untereiner A, Wu L, Yang G, Austin RC, Dickhout JG, Lhoták Š, Meng QH, Wang R (2013) Decreased endogenous production of hydrogen sulphide accelerates atherosclerosis.

Circulation 127(25):2523–2534. https://doi.org/10.1161/CIRCULATIONAHA.113.002208. Epub 2013 May 23

Manna P, Jain SK (2013) L-cysteine and hydrogen sulphide increase PIP3 and AMPK/PPARγ expression and decrease ROS and vascular inflammation markers in high glucose treated human U937 monocytes. J Cell Biochem 114(10):2334–2345. https://doi.org/10.1002/jcb.24578

Manna P, Gungor N, McVie R, Jain SK (2014) Decreased cystathionine-γ-lyase (CSE) activity in livers of type 1 diabetic rats and peripheral blood mononuclear cells (PBMC) of type 1 diabetic patients. J Biol Chem 289(17):11767–11778. https://doi.org/10.1074/jbc.M113.524645. Epub 2014 Mar 7

Marutani E, Yamada M, Ida T, Tokuda K, Ikeda K, Kai S, Shirozu K, Hayashida K, Kosugi S, Hanaoka K, Kaneki M, Akaike T, Ichinose F (2015) Thiosulphate mediates cytoprotective effects of hydrogen sulphide against neuronal ischemia. J Am Heart Assoc 4(11):pii: e002125. https://doi.org/10.1161/JAHA.115.002125

Matz H, Orion E, Wolf R (2003) Balneotherapy in dermatology. Dermatol Ther 16(2):132–140

McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K, Lohmander S, Rannou F, Roos EM, Underwood M (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartil 22(3):363–388. https://doi.org/10.1016/j.joca.2014.01.003. Epub 2014 Jan 24

Nagpure BV, Bian JS (2014) Hydrogen sulphide inhibits A2A adenosine receptor agonist induced β-amyloid production in SH-SY5Y neuroblastoma cells via a cAMP dependent pathway. PLoS One 9(2):e88508. https://doi.org/10.1371/journal.pone.0088508. eCollection 2014

Naumann J, Sadaghiani C (2014) Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. Arthritis Res Ther 16(4):R141. https://doi.org/10.1186/ar4603

Nicholson CK, Calvert JW (2010) Hydrogen sulphide and ischemia-reperfusion injury. Pharmacol Res 62(4):289–297. https://doi.org/10.1016/j.phrs.2010.06.002. Epub 2010 Jun 11. Review

Nugraha B, Neues-Lahusen M, Candir F, Gutenbrunner C (2011) Effect of a series of H_2S mineral water bathing on pain in patients with fibromyalgia syndrome – a pilot study. Physikalische Medizin Rehabilitationsmedizin Kurortmedizin 21(06):284–289

Nuvolone D, Petri D, Pepe P, Voller F (2019) Health effects associated with chronic exposure to low-level hydrogen sulphide from geothermoelectric power plants. A residential cohort study in the geothermal area of Mt. Amiata in Tuscany. Sci Total Environ 659:973–982. https://doi.org/10.1016/j.scitotenv.2018.12.363. Epub 2018 Dec 27

Ottaviano G, Marioni G, Staffieri C, Giacomelli L, Marchese-Ragona R, Bertolin A, Staffieri A (2011) Effects of sulphurous, salty, bromic, iodic thermal water nasal irrigations in nonallergic chronic rhinosinusitis: a prospective, randomized, double-blind, clinical, and cytological study. Am J Otolaryngol 32(3):235–239. https://doi.org/10.1016/j.amjoto.2010.02.004. Epub 2010 May 26

Pan LL, Liu XH, Gong QH, Wu D, Zhu YZ (2011) Hydrogen sulphide attenuated tumor necrosis factor-α-induced inflammatory signaling and dysfunction in vascular endothelial cells. PLoS One 6(5):e19766. https://doi.org/10.1371/journal.pone.0019766

Papapetropoulos A, Pyriochou A, Altaany Z, Yang G, Marazioti A, Zhou Z, Jeschke MG, Branski LK, Herndon DN, Wang R, Szabó C (2009) Hydrogen sulphide is an endogenous stimulator of angiogenesis. Proc Natl Acad Sci U S A 106(51):21972–21977. https://doi.org/10.1073/pnas.0908047106. Epub 2009 Dec 2

Paul BD, Snyder SH (2015) H2S: a novel Gasotransmitter that signals by Sulfhydration. Trends Biochem Sci 40(11):687–700. https://doi.org/10.1016/j.tibs.2015.08.007. Epub 2015 Oct 1

Paul BD, Sbodio JI, Xu R, Vandiver MS, Cha JY, Snowman AM, Snyder SH (2014) Cystathionine γ-lyase deficiency mediates neurodegeneration in Huntington's disease. Nature 509(7498):96–100. https://doi.org/10.1038/nature13136. Epub 2014 Mar 26

Pellegrini M, Fanin D, Nowicki Y, Guarnieri G, Bordin A, Faggian D, Plebani M, Saetta M, Maestrelli P (2005) Effect of inhalation of thermal water on airway inflammation in chronic obstructive pulmonary disease. Respir Med 99(6):748–754. Epub 2004 Dec 13

Perry MM, Hui CK, Whiteman M, Wood ME, Adcock I, Kirkham P, Michaeloudes C, Chung KF (2011) Hydrogen sulphide inhibits proliferation and release of IL-8 from human airway smooth muscle cells. Am J Respir Cell Mol Biol 45(4):746–752. https://doi.org/10.1165/rcmb.2010-0304OC. Epub 2011 Feb 4

Prandelli C, Parola C, Buizza L, Delbarba A, Marziano M, Salvi V, Zacchi V, Memo M, Sozzani S, Calza S, Uberti D, Bosisio D (2013) Sulphurous thermal water increases the release of the anti-inflammatory cytokine IL-10 and modulates antioxidant enzyme activity. Int J Immunopathol Pharmacol 26(3):633–646

Qian LL, Liu XY, Chai Q, Wang RX (2018) Hydrogen Sulphide in diabetic complications: focus on molecular mechanisms. Endocr Metab Immune Disord Drug Targets 18(5):470–476. https://doi.org/10.2174/1871530318666180426100532

Qipshidze N, Metreveli N, Mishra PK, Lominadze D (2012) Hydrogen sulphide mitigates cardiac remodeling during myocardial infarction via improvement of angiogenesis. Int J Biol Sci 8(4):430–441. https://doi.org/10.7150/ijbs.3632. Epub 2012 Feb 28

Safar MM, Abdelsalam RM (2015) H2S donors attenuate diabetic nephropathy in rats: modulation of oxidant status and polyol pathway. Pharmacol Rep 67(1):17–23. https://doi.org/10.1016/j.pharep.2014.08.001. Epub 2014 Aug 20

Salami A, Dellepiane M, Crippa B, Mora F, Guastini L, Jankowska B, Mora R (2008) Sulphurous water inhalations in the prophylaxis of recurrent upper respiratory tract infections. Int J Pediatr Otorhinolaryngol 72(11):1717–1722. https://doi.org/10.1016/j.ijporl.2008.08.014. Epub 2008 Sep 24

Salami A, Dellepiane M, Strinati F, Guastini L, Mora R (2010) Sulphurous thermal water inhalations in the treatment of chronic rhinosinusitis. Rhinology 48(1):71–76. https://doi.org/10.4193/Rhin09.065

Santos I, Cantista P, Vasconcelos C, Amado J (2016) Balneotherapy and rheumatoid arthritis: a randomized control trial. Isr Med Assoc J 18(8):474–478

Sellak H, Choi CS, Dey NB, Lincoln TM (2013) Transcriptional and post-transcriptional regulation of cGMP-dependent protein kinase (PKG-I): pathophysiological significance. Cardiovasc Res 97(2):200–207. https://doi.org/10.1093/cvr/cvs327. Epub 2012 Nov 8

Sen N (2017) Functional and molecular insights of hydrogen sulphide signaling and protein sulfhydration. J Mol Biol 429(4):543–561. https://doi.org/10.1016/j.jmb.2016.12.015. Epub 2016 Dec 21

Skrtic L (2006) Hydrogen sulfide, oil and gas, and people's health. Master's of Science. Energy and Resources Group, University of California, Berkeley, 2006: 1–77

Štambuk-Giljanović N (2008) Characteristics and origin of the hydrogen sulphide spring water from the Split spa (Southern Croatia). Environ Monit Assess 140:109–117. https://doi.org/10.1007/s10661-007-9852-6

Steudler PA, Peterson BJ (1984) Contribution of gaseous sulphur from salt marshes to the global sulphur cycle. Nature 311:455–457

Sukenik S, Flusser D, Abu-Shakra M (1999) The role of spa therapy in various rheumatic diseases. Rheum Dis Clin N Am 25:883–897

Sukenik S, Buskila D, Neumann L, Kleiner-Baumgarten A, Zimlichman S, Horowitz J (1990) Sulphur bath and mud pack treatment for rheumatoid arthritis at the Dead Sea area. Ann Rheum Dis 49(2):99–102

Sun CC, Sue MS (1995) Sulphur spring dermatitis. Contact Dermatitis 32(1):31–34

Sun L, Zhang S, Yu C, Pan Z, Liu Y, Zhao J, Wang X, Yun F, Zhao H, Yan S, Yuan Y, Wang D, Ding X, Liu G, Li W, Zhao X, Liu Z, Li Y (2015) Hydrogen sulphide reduces serum triglyceride by activating liver autophagy via the AMPK-mTOR pathway. Am J Physiol Endocrinol Metab 309(11):E925–E935. https://doi.org/10.1152/ajpendo.00294.2015. Epub 2015 Oct 6

Suzuki K, Sagara M, Aoki C, Tanaka S, Aso Y (2017) Clinical implication of plasma hydrogen sulphide levels in Japanese patients with type 2 diabetes. Intern Med 56(1):17–21. https://doi.org/10.2169/internalmedicine.56.7403. Epub 2017 Jan 1

Tang G, Wu L, Liang W, Wang R (2005) Direct stimulation of K(ATP) channels by exogenous and endogenous hydrogen sulphide in vascular smooth muscle cells. Mol Pharmacol 68(6):1757–1764. Epub 2005 Sep 8

Toussaint C, Peuchant E, Nguyen BC, Jensen R, Canellas J (1986) Influence of calcic and magnesic sulphurous thermal water on the metabolism of lipoproteins in the rat. Arch Int Physiol Biochim 94(2):65–76

US National Research Council (1979) Subcommittee on hydrogen sulfide. University Park Press, Baltimore

Valenzuela MA (1968) Compêndio de Hidrologia Médica, Ed. Científico – Médico, Barcelona

Vandiver MS, Paul BD, Xu R, Karuppagounder S, Rao F, Snowman AM, Ko HS, Lee YI, Dawson VL, Dawson TM, Sen N, Snyder SH (2013) Sulfhydration mediates neuroprotective actions of parkin. Nat Commun 4:1626. https://doi.org/10.1038/ncomms2623

Varricchio A, Giuliano M, Capasso M, Del Gaizo D, Ascione E, De Lucia A, Avvisati F, Capuano F, De Rosa G, Di Mauro F, Ciprandi G (2013) Salso-sulphide thermal water in the prevention of recurrent respiratory infections in children. Int J Immunopathol Pharmacol 26(4):941–952

Verhagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, de Bie R, de Vet HC (2015) Balneotherapy (or spa therapy) for rheumatoid arthritis. Cochrane Database Syst Rev (4):CD000518. https://doi.org/10.1002/14651858.CD000518.pub2

Wakabayashi N, Dinkova-Kostova AT, Holtzclaw WD, Kang MI, Kobayashi A, Yamamoto M, Kensler TW, Talalay P (2004) Protection against electrophile and oxidant stress by induction of the phase 2 response: fate of cysteines of the Keap1 sensor modified by inducers. Proc Natl Acad Sci U S A 101(7):2040–2045. Epub 2004 Feb 5

Wallace JL, Ferraz JG, Muscara MN (2012) Hydrogen sulphide: an endogenous mediator of resolution of inflammation and injury. Antioxid Redox Signal 17(1):58–67. https://doi.org/10.1089/ars.2011.4351. Epub 2011 Dec 15

Wang X, Wang Q, Guo W, Zhu YZ (2011) Hydrogen sulphide attenuates cardiac dysfunction in a rat model of heart failure: a mechanism through cardiac mitochondrial protection. Biosci Rep 31(2):87–98. https://doi.org/10.1042/BSR20100003

Wetzel MD, Wenke JC (2019) Mechanisms by which hydrogen sulphide attenuates muscle function following ischemia-reperfusion injury: effects on Akt signaling, mitochondrial function, and apoptosis. J Transl Med 17(1):33. https://doi.org/10.1186/s12967-018-1753-7

WHO (World Health Organization) (1981) Hydrogen sulfide. Geneva, Environmental Health Criteria. 1981 No. 19

WHO (World Health Organization) (2000) Chapter 6.6 Hydrogen sulfide. In: Air quality guidelines, 2nd edn. WHO Regional Office for Europe, Copenhagen

World Health Organization (2003) Concise International Chemical Assessment Document 53, Hydrogen sulphide: human health Aspects

Xiao T, Luo J, Wu Z, Li F, Zeng O, Yang J (2015) Effects of hydrogen sulphide on myocardial fibrosis and PI3K/AKT1-regulated autophagy in diabetic rats. Mol Med Rep 13(2):1765–1773. https://doi.org/10.3892/mmr.2015.4689. Epub 2015 Dec 17

Xu S, Liu Z, Liu P (2014) Targeting hydrogen sulphide as a promising therapeutic strategy for atherosclerosis. Int J Cardiol 172(2):313–317. https://doi.org/10.1016/j.ijcard.2014.01.068. Epub 2014 Jan 24

Xu W, Chen J, Lin J, Liu D, Mo L, Pan W, Feng J, Wu W, Zheng D (2015) Exogenous H_2S protects H9c2 cardiac cells against high glucose-induced injury and inflammation by inhibiting the activation of the NF-κB and IL-1β pathways. Int J Mol Med 35(1):177–186. https://doi.org/10.3892/ijmm.2014.2007. Epub 2014 Nov 19

Yang G, Yang W, Wu L, Wang R (2007) H_2S, endoplasmic reticulum stress, and apoptosis of insulin-secreting beta cells. J Biol Chem 282(22):16567–16576. Epub 2007 Apr 12

Yang G, Wu L, Jiang B, Yang W, Qi J, Cao K, Meng Q, Mustafa AK, Mu W, Zhang S, Snyder SH, Wang R (2008) H_2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. Science 322(5901):587–590. https://doi.org/10.1126/science.1162667

Yang CT, Zhao Y, Xian M, Li JH, Dong Q, Bai HB, Xu JD, Zhang MF (2014) A novel controllable hydrogen sulphide-releasing molecule protects human skin keratinocytes against methylglyoxal-induced injury and dysfunction. Cell Physiol Biochem 34(4):1304–1317. https://doi.org/10.1159/000366339. Epub 2014 Sep 29

Yu XH, Cui LB, Wu K, FS ZXLC, Chen ZW, Tang CK (2014) Hydrogen sulphide as a potent cardiovascular protective agent. Clin Chim Acta 437:78–87. https://doi.org/10.1016/j.cca.2014.07.012. Epub 2014 July 21

Yurtkuran M, Yurtkuran M, Alp A, Nasircilar A, Bingöl U, Altan L, Sarpdere G (2006) Balneotherapy and tap water therapy in the treatment of knee osteoarthritis. Rheumatol Int 27(1):19–27. Epub 2006 July 11

Zhen Y, Pan W, Hu F, Wu H, Feng J, Zhang Y, Chen J (2015) Exogenous hydrogen sulphide exerts proliferation/anti-apoptosis/angiogenesis/migration effects via amplifying the activation of NF-κB pathway in PLC/PRF/5 hepatoma cells. Int J Oncol 46(5):2194–2204. https://doi.org/10.3892/ijo.2015.2914. Epub 2015 Mar 3

Zwolińska JI, Weres AI, Wyszyńska JI (2018) One-year follow-up of spa treatment in older patients with osteoarthritis: a prospective, single group study. Biomed Res Int 2018:7492106. https://doi.org/10.1155/2018/7492106. E Collection 2018

Chapter 16
Salt Mineral Water and Thalassotherapy

Celso S. F. Gomes, João V. Fernandes, Filomena V. Fernandes, and João B. P. Silva

Abstract Thalassotherapy, actually defined as the combined use of the preventive and therapeutic purposes of seawater and sea-derived products under counseling and medical supervision inside the adequate facilities of establishments located nearby the sea, has deserved the interest of many researchers. The chapter reports the historical foregoing, the concepts, the physical and chemical properties, and the application methods of seawater and of its derived products (mud, sand, algae, salt, aerosols, etc.) for therapeutic purposes. Human health benefits provided by thalassotherapy result from the minerals, either dissolved in seawater or participating in the chemical composition of sea-derived products: mud, sand, salt, and marine aerosol. Thalassotherapy is one of the main byproducts of health and wellness tourism programs that comprise healthy activities such as *thermalism/crenotherapy*, *mudtherapy/pelotherapy*, *psammotherapy* or *arenotherapy*, *halotherapy*, and *climatotherapy*. The therapeutic effects of seawater and sea-derived products and methods, such as halotherapy, hydrohalotherapy, hydrohalotheray, plus mudtherapy, as well as legislation, accreditation, and certification of thalasso centers, are dealt with too.

C. S. F. Gomes (✉) · J. B. P. Silva
Department of Geosciences, Researcher of the Research Unit "GeoBioTec", University of Aveiro, Aveiro, Portugal
e-mail: cgomes@ua.pt; madeirarochas@netmadeira.com

J. V. Fernandes
AMTSBE (Association Mondiale de Tourisme de Santé et Bien-Être), Researcher and Consultant, University of Algarve, Faro, Portugal
e-mail: healthwellnesstourism.amtsbe@gmail.com

F. V. Fernandes
Physician, Expert in Public Health, Urbanização S.Luis, Faro, Portugal
e-mail: healthwellnesstourism.amtsbe@gmail.com

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2_16

16.1 Concepts and Historical Information

The term *thalassotherapy* stems from the Greek word *thálassa* (θάλασσα) meaning sea or ocean. Today *thalassotherapy* by definition is the use of seawater, sea products (sand, mud, salt, algae, aerosols, etc.), and seaside climate as a form of therapy. However, the actual definition of *thalassotherapy* is more precise considering the combined use of the preventive and therapeutic purposes of seawater and sea-derived products, under counseling and medical supervision, inside the adequate facilities of establishments located nearby the sea. The holistic concept of *thalassotherapy* should contemplate too the controlled physical exercise and the alimentary reeducation.

There is a significant number of scientific publications on *thalassotherapy* deserving to be enhanced which are written by the following authors: Pros (1980), Hobel (1985), San Martin (1995), Sukenik et al. (1995, 1999), Hoareau (2002), Flusser et al. (2002), Tréguer (2003), São José (2004), Duparc-Ricoux et al. (2004), Codish et al. (2005), Zijlstra et al. (2005), Tinghérian (2005), Cerrada (2007), Caselles (2007), Lucchetta et al. (2007), de Andrade et al. (2008), Kazandjieva et al. (2008), Charlier and Chaineux (2009), Schuh (2009), Czarnowicki et al. (2011), Bonsignori (2011), Rogozian et al. (2011), Veillet-Berry (2011), Viegas Fernandes and Viegas Fernandes (2011), Katz et al. (2012), Kopel et al. (2013), Alberola and Coll (2013), Abu-Shakra et al. (2014), Maraver (2000, 2015), Morer (2016), Morer et al. (2017a, b), Gomes et al. (2019), and Munteanu and Munteanu (2019). The last scientific publication referred to intends to be a systematic and summarizing review of all published articles related to the thalassotherapy and thermal medicine subject found in *Web of Science Core Collection*.

About thalassotherapy the very recent paper by Morer (2016) reports the historical foregoing, the concepts, the physical and chemical properties, and the application methods of seawater and of its derived products (mud, sand, algae, salt, aerosols, etc.) for therapeutic purposes.

Human health benefits provided by thalassotherapy result from the minerals, either dissolved in seawater or participating in the chemical composition of sea-derived products: mud, sand, salt, and marine aerosol. All the treatments involving the resources referred to have health indications and contraindications, the reason why the counseling and supervision of properly specialized medical staff are fundamental requisites. The individual use for preventive and therapeutic purposes and under medical supervision of any of aforesaid sea products should not be called thalassotherapy, unless it takes place inside the facilities of a *thalasso center* where the use of seawater is necessarily practiced too. As a rule, seawater and its derived products, sand, mud, and salt, are therapeutically used in separate *thalassotherapy*, *psammotherapy*, *mudtherapy/pelotherapy*, and *halotherapy spas*.

Only exceptionally, seawater and its sand and mud products are used together in the same thalasso center for therapeutic purposes. In the Murcia region, in the lagoon of Mar Menor, more precisely in Lo Pagán, San Pedro del Pinatar, there is a quite significant number of balnearies where seawater and sea mud are used in the same establishment, naturally in distinct and adequate facilities, for therapeutic purposes.

France was the pioneer country of scientific *thalassotherapy*. The first seawater healthcare facility was established in 1778, in Dieppe, France.

The term *thalassotherapy* is due to Dr. De la Bonnardière, in 1867, for the medicinal use of seawater in a resort, in Arcachon, France. Later, in 1899, Dr. Louis Bagot created the first thalassotherapy center, in Roscoff, France. Also, the French biologist René Quinton, in 1904, found out the organic identity between seawater and the blood plasma of the human being.

Greeks and Romans venerate Neptune and Poseidon, respectively, as the gods of the seas, and both Greek and Roman civilizations have used the healing powers of seawater. Already Eurípides (480–406 B.C.), a Greek poet, said, "The sea cures all man diseases." Hippocrates (460–370 B.C.) also said that, "Taken as baths seawater is good for skin itching and prickning; it is also good under the form of vapours, without neglecting unctions, poultices of marine plant leaves, compresses; it is advantageous in the treatment of wounds…."

Hippocrates, considered as the "father of medicine," had prescribed treatments based on seawater, either for ingestion or under the form of external applications (baths and ablutions). Also, Polybius (205–120 B.C.), a Greek chronicler, said: "Everything in the sea is beneficial, it was the origin of the human being and continues to watch over his health."

The Phoenician, the Greek, and the Romans have taken health advantages of the sea's prophylactic and therapeutic properties.

Lucchetta et al. (2007) report the historical development of sea medicine from the ancient Egyptians until the twentieth century. The authors state that the medical world has viewed it with different opinions, from very enthusiastic to extremely critical, and from beneficial to harmful, and that in the last decades, thalassotherapy is receiving renewed attention from many medical specialties and health tourists. The aim of this review is to offer an update on the real therapeutic possibility of the thalassotherapy. However, the exact therapeutic potential of thalassotherapy still remains largely unknown. Better and more profound scientific evidence for its efficacy is therefore warranted, in particular for its effects on the musculoskeletal system and on the skin. The main researches are concerned with the activity of thalassotherapy and the clinical outcomes, namely, in patients suffering from osteoarthritis.

The sea is a source of health and wellbeing, since seawater, among all mineral waters, is the richest in minerals, containing all (92) natural chemical elements.

The breathing of ocean air loaded with negative ions will have several therapeutic effects (against asthma, sinusitis, skin diseases, allergies, heart diseases) as well as anti-inflammatory and relaxing properties for some mental and psychological diseases.

Figure 16.1 shows the average chemical composition of seawater. Sodium chloride (NaCl) is the fundamental constituent of seawater, representing about 80% of total dissolved salts, the other salts being sulfates, bicarbonates, bromides, fluorides, and silicates. Ca, Mg, K, Br, B, F, Si, and more 79 oligoelements are present

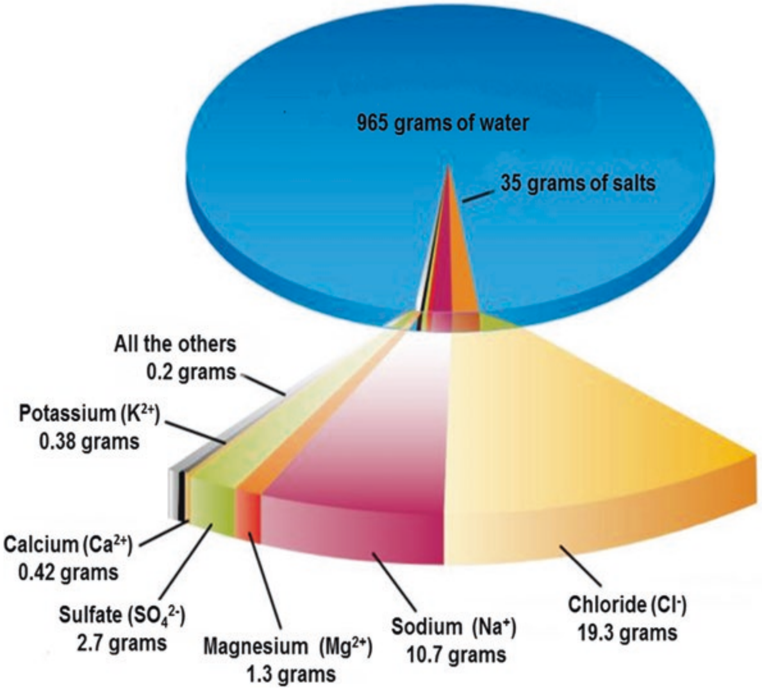


Fig. 16.1 Average chemical composition of seawater; weights (in grams) of the main minerals dissolved in one kilogram of seawater

too, as well all gases present in the atmosphere, and within them N, O, and CO_2 are the most abundant.

The chemical composition of seawater is almost similar to human blood plasma, although the concentration of the mineral salts is three times higher. There are products, such as nasal sprays used in healthcare, exemplified by one commercialized under the name Rhinomer, composed of natural seawater duly sterilized after dilution to the reduced content of 9 g/L NaCl, i.e., isotonic seawater. Our nose acts as a filter protector. About 10,000 L/day of air are inspired, air containing various impurities that can cause nasal irritations and increase nasal mucosa secretion.

The chemical composition of water from seas and oceans is not uniform, varying within narrow limits, depending on regional geology and climate.

Have shown the existing differences, in terms of chemical and physicochemical parameters, between the Atlantic Ocean water sampled right in front of the south coast beach of Porto Santo Island from the Madeira archipelago and the reference ocean water.

Seawater temperature varies from −4 °C in the Arctic sea up to 30 °C in tropical zones, and seawater density varies from 1,028 g/L up to 1,032 g/L. In Porto Santo Island seawater is warm all year round, 19–20 °C in winter and 22–24 °C in summer.

16.2 Thalassotherapy in Portugal

Portugal has not been taking advantage of the enormous potentialities that thalassotherapy could represent. It should be noted that Portugal due to its geographic location, surrounded by the Atlantic Ocean, has better conditions for the practice of thalassotherapy due to the quality of seawater, sea breezes, algae/seaweeds, sands, and muds.

We would like to point out that the seven Lusophone countries have extensive coastlines with enormous potential to develop thalassotherapy. The implementation of thalassotherapy could make a valuable contribution to the sustainable development of those countries and to the improvement of the quality of life and health of the native populations.

The Portuguese coastline reaches 1792 km of which the archipelagos of Madeira and the Azores contribute with 960 km. The Atlantic coast of mainland Portugal is 832 km. Tunisia, the second thalassotherapy tourist destination, with more than 60 (sixty) thalasso centers, has 1298 km of Mediterranean coastline. Most tourist destinations with thalassotherapy, as Tunisia, are only bathed by the Mediterranean Sea.

In the littoral zone of the Portugal continent, there are population aggregates of varied size and excellent climatic, landscape, and accessibility conditions for the installation of thalassotherapy establishments, and it is clear that the number of centers referred to is very small (Gameiro 2011). Portugal has a total coastline estimated at 1792 km, including the coastline of mainland of Portugal and the coastline of the islands of the archipelagos of Madeira and the Azores, 832 km in the mainland and 960 km in the whole of of the islands. The mainland alone, along the seashore has a significant number of population aggregates of varied size, and the excellent climate, landscape, and accessibility gathers privileged conditions for the installation of thalassotherapy establishments, in number that could be much higher than the actual number of existing Thalasso Centres.

Presently in Portugal the sea economy represents about 3% of the GIP, a value that could be easily maximized taking advantage of the actual and future scientific and technological knowledge. Mapping of the seafloor using drones and robots needs to be thoroughly carried out when looking at the identification and characterization of the ecosystems, in order to find out how they work, how they could be exploited, and how they could be protected.

Viegas Fernandes and Viegas Fernandes (2011) mention the existence of countries where *thalassotherapy* is much divulged and practiced in *thalassotherapy centers* or *thalasso centers* and in *thalassotherapy Spas*, the last preferably hosted in hotel units. Relative to the number of thalasso centers, the figures are as follows: France, 60; Spain, 57; Tunisia, 40; Italy, 27; Turkey, 12; and the USA, 10.

Portugal with its Atlantic coastline of 1792 km has only six *thalasso centers*: *Grande Real Santa Eulália Resort & Hotel Spa*, Algarve; *Sofitel Thalassa Vilalara Resort*, Algarve; *Thalasso Costa da Caparica*, Costa da Caparica; *seaside resort of Espinho city hall*, Espinho; *Barra Talasso*, *SA*, Nazaré; and *Vila Baleira Resort*, Porto Santo Island, Madeira. In Funchal, Madeira Island of the Madeira Archipelago, there is one hotel spa, Vidamar Resort Hotel Madeira Thalasso Sea & Spa, where seawater is used for wellbeing purposes.

The Porto Santo Island of the Madeira Archipelago, at the worldwide scale, is one of the very rare territories where in the same *thalasso center* seawater and sea-derived products as sand, mud, algae, etc. could be used together, naturally in separate and adequate individual facilities.

In particular, the Porto Santo Island possesses natural resources with origin in the sea whose particular specificities are of paramount potential importance for thalassotherapy purposes and applications. Also, the Porto Santo Island is one territory where nature that is almost unspoiled needs to be preserved. In fact, the island requires responsible tourism and sustainability, being well established that the principal ingredients for sustainability are nature and culture. The characteristics of such natural resources are well documented in the bilingual book entitled *Ilha do Porto Santo: Estância Singular de Saúde Natural* (Porto Santo Island: Unique Natural Health Resort) by Gomes and Silva (2012). Worldwide general information about thalassotherapy and in particular about thalassotherapy in Porto Santo' Island has been recently published (Gomes et al. 2019).

Another very interesting natural resource of Porto Santo is the mild oceanic climate that prevails in the island all year round as well as the characteristic fragrance of marine aerosol. The particular climate features and the health benefits of *climatotherapy* have been studied and reported (Gomes and Silva 2012).

The following meteorological data determined in the island are herein enhanced: 16 °C is the minimum annual value of air temperature measured in February, and 24 °C is the maximum measured in August; the mean annual value of thermal amplitude is estimated at 7 °C; 18 °C is the minimum mean annual value of seawater temperature in February, and 24 °C is the maximum mean annual value measured in October; for long periods of time seawater temperature is higher than air temperature. However, much more investigation on the health effects of local *climatotherapy* is needed.

Actually, in Porto Santo Island, thalassotherapy is only practiced in Vila Baleira Hotel & Thalasso spa where seawater applications do take place in facilities adequately equipped to achieve the expected health benefits.

Figure 16.2 shows some details of the facilities of the Vila Baleira Thalasso Hotel & Thalasso spa. The photograph was taken during a visit included in the I World Health and Wellness Tourism Congress organized by the WHWTA (World Health and Wellness Tourism Association) and held in Madeira and Porto Santo islands of the Madeira archipelago, 1–4 October 2018.

About thalassotherapy the very recent paper by Morer (2016) reports the historical foregoing, the concepts, the physical and chemical properties, and the application methods of seawater and of its derived products (mud, sand, algae, salt, aerosols, etc.) for therapeutic purposes.

Viegas Fernandes and Viegas Fernandes (2014) have been developing research on 300 (three hundred) thalasso centers worldwide and identified the main important countries: France, Tunisia, and Spain (about 60 *thalasso centers* for each country), Italy (30 centers), and Romania. Also, Viegas Fernandes and Viegas Fernandes

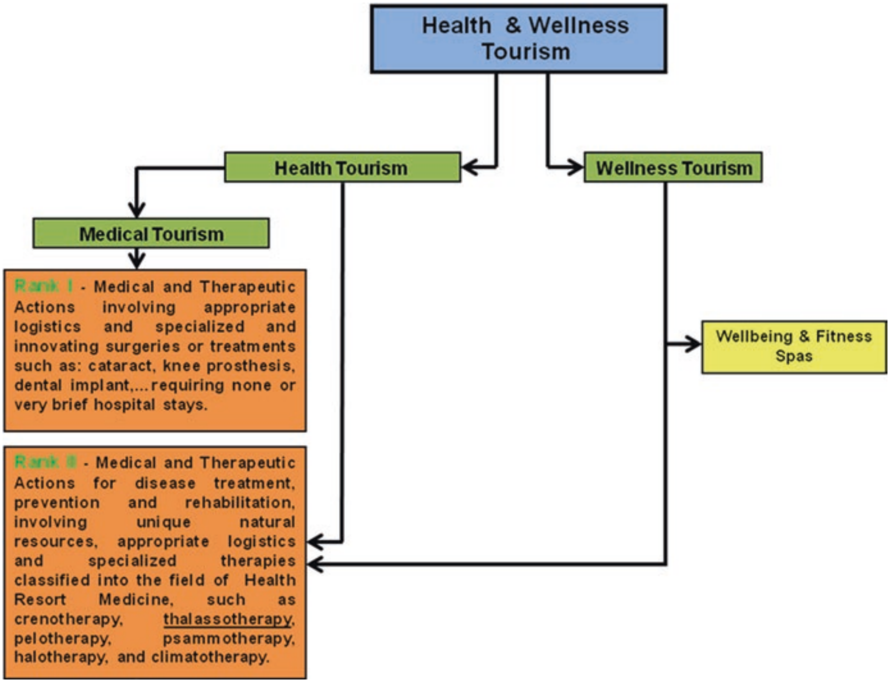
Fig. 16.2 View of the thalasso spa of Vila Baleira Hotel, in Porto Santo Island

(2011) report information s about the traditional attraction of the so-called sacred sea baths in Portugal, which the authors admit to go back to the time of the Arabs who had the ancestral tradition of water worship and who, after the Christian reconquest was continued, with annual baths celebrated in the Algarve on 24 June or 29 August.

16.3 Thalassotherapy as a Byproduct of Health and Wellness Tourism

Thalassotherapy is one of the main byproducts of health and wellness tourism programs (Fig. 16.3) that comprises healthy activities such as *thermalism/crenotherapy*, using natural mineral water and natural mud/peloid in thermal resorts as healthy resources; *mudtherapy/pelotherapy*, using mud/peloid that as a rule could be derived from the sea or from natural mineral water, as healthy resource; *psammotherapy or arenotherapy* , using special natural sands that as a rule derived from the sea, as healthy resource; *halotherapy*, using sea salt as healthy resource; and *climatotherapy*, using seaside climate as healthy resource.

The essence of *health and wellness tourism* is that health and wellness tourists travel from the place where they live to another place looking for healthcare able to improve their health and wellness, all requiring qualified medical intervention provided for periods ranging from few days to few weeks.



Rank I - Medical and Therapeutic Actions involving appropriate logistics and specialized and innovating surgeries or treatments such as: cataract, knee prosthesis, dental implant,....requiring none or very brief hospital stays.

Rank II - Medical and Therapeutic Actions for disease treatment, prevention and rehabilitation, involving unique natural resources, appropriate logistics and specialized therapies classified into the field of Health Resort Medicine, such as crenotherapy, thalassotherapy, pelotherapy, psammotherapy, halotherapy, and climatotherapy.

Fig. 16.3 Diagram showing thalassotherapy as a subcategory of medical tourism within the global framework of health and wellness tourism

Health and wellness tourism is a fast-growing market of high economic and social significance, and it includes two main categories:

1. *Health tourism*
2. *Wellness tourism*

Health tourism includes two ranks or subcategories:

Rank I – Medical tourism (involving appropriate logistics, specialized physicians and medical teams, and innovating surgeries or treatments, all requiring, as a rule, very short stays, few days to few weeks, in hospitals); *medical tourism* is defined as, "The travel with the purpose of improving well-being and receiving medical services and care outside one's region" (Burkett 2007; Connell 2006; Lunt et al. 2011).

Rank II – Medical and wellness tourism (involving unique natural resources, appropriate logistics, and medical teams specializing on public health and therapies all classified into the field of *health and wellness* and provided in *health resorts*, for instance, in the so-called *thermal resort spas*, *thalassotherapy spas*, *psammotherapy spas*, *mudtherapy spas, pelotherapy spas*, and *climatotherapy spas*, as a rule, for 2–3 weeks).

The goal of both subcategories in treatment and prevention of disease is the same: “To die young, but as late as possible” (Dr. Helmut Pratzel, ex-President of ISMH).

Medical and wellness tourism comprises a set of activities: *thermalism and crenotherapy* (using natural mineral waters as healthy resources), *thalassoteraphy* (using natural products of the sea, water, algae, mud, and salt as healthy resources), *psammotherapy* (using special natural sands as healthy resources), *mudtherapy and pelotherapy* (using muds and peloids as healthy resources), and *climatotherapy* (using climate as healthy resource), all provided in health resorts. All these activities have health as the main target and use unique natural resources as the basis or support to improve both physical and mental wellness of individuals (patients).

In *medical and wellness tourism*, travel is associated with the pursuit of maintaining or enhancing one’s personal wellbeing (Burkett 2007; Vaselova 2017).

The term wellness, with origin in the USA, has been defined as the pursuit of a healthy body and mind, particularly carried out inside the specific environments of the so-called wellness *spas*. There are diverse wellness spa typologies, some not having medical assistance and some not requiring the use of water (fitness spa, halo spa, sports spa, etc.).

Medical and wellness tourism comprises activities addressed to disease cure, prevention, and rehabilitation that could be provided in *health resorts*, for instance, at the so-called thermal resorts located, as a rule, in nonurban areas and in sites possessing highly attractive natural resources (high-quality environment, healthy climate, exotic landscape, ecologic parks, and walking areas), archaeological and architectonic patrimony, excellent logistics (duly equipped balnearies), human resources (qualified medical and technical), and areas for aesthetic, fitness, and relaxation.

Natural mineral water – Ingested, inhaled, and/or topically applied; seawater, natural gases (CO_2, H_2S, and Rn), and *peloids* are the natural resources currently used in thermal resorts.

Health resort medicine practiced in thermal resorts is used by those who are looking for cure or temporary improvement of rheumatic, digestive, metabolic, respiratory, and dermatologic diseases.

Associated with all the resorts referred to, activities of aesthetic care, cosmetics, healthy nutrition, relaxation, and mental dynamics could be provided in the so-called wellness spas that could be integrated too into the field of health tourism, since they could provide healthcare activities complimentary to those usually carried out in those resorts. Qualified medical and technical assistance is required in all *health resorts* referred to, as well as in *wellness spas*.

Public health is the goal of present-day *health resort medicine* whose targets are as follows:

1. Prevention is better than therapy.
2. Learning to live healthfully.

The ISPA (International Spa Association), in 2007, defines *spa* as a place devoted to enhance overall wellbeing through a variety of professional services that encourage the renewal of body, mind, and spirit.

Nowadays *health tourism* of Rank II and *wellness tourism* is considered a strategic product, inextricably linked to *thermal resorts*.

In Portugal, the Decreto-Lei 142/2004 of June 11 regulates the activity of thermal resorts attributing to them an essential role on the tourism sector. Revitalization of thermal resorts much depends on the diversification of their offers involving the balance or equilibrium between therapeutic activities and wellbeing and leisure activities. Thermal resort restructuring requires a development model based on the completeness of *classic therapeutics* and *health and wellness* segments with the segment of *tourism and recreation*. Also, a more effective *product differentiation* is required too, in order to become attractive and competitive.

In what *wellbeing and fitness spa* is concerned for non-European countries, American countries in particular, what characterizes one *spa* is the individual promotion of both *wellbeing,* mainly in terms of aesthetics and cosmetics, and mental and physical *fitness,* using methods and techniques of disease prevention, rehabilitation, and therapy (treatments with natural products) – a concept of the ISPA (International Spa & Fitness Association).

Massages (holistic and recover), aesthetic treatments (facial masks, anti-cellulite), detox treatments, techniques of physical and mental relaxing, hydrotherapy, and gymnasium fitness are some of the activities applied in *wellbeing and fitness spas*, quite common in urban areas (particularly in hotels) and where clinical treatments are dispensable. On the contrary, as a rule, these therapeutic treatments with medical assistance are essential on traditional *thermal resorts* and on *wellness spas* too.

16.4 Therapeutic Use of Seawater and Sea-Derived Products

In practical terms it is recognized that the practice of *thalassotherapy*, when seawater is applied externally, particularly through thermal and mechanical effects, stimulates blood circulation, ensures muscle relaxation, reduces stress, and also has anti-pain and anti-inflammatory effects. However, seawater can also be administered internally, ingested or nebulized, as is the case with the *natural mineral water* used for therapeutic purposes in the bathhouses of *spa thermal resorts*.

Studies conducted by US scientists have shown that the application of seawater-rich aerosols, containing sodium chloride and various other salts, or hypertonic solutions, has positive effects on the disease called cystic fibrosis or cystic fibrosis affecting the lungs, which is heredity and causes mortality.

Spas (*salutem per aqua*), currently of flourishing implantation in Portugal, are *welfare centers*, which include *hydrotherapy*, *thalassotherapy*, and *aesthetic* treatments.

Viegas Fernades and Viegas Fernandes (2011) had identified 255 (two hundred fifty-five) *spas* in Portugal, about 200 (two hundred) integrated in hotel establishments, using water for human consumption, or better tap water; about 40 (forty) integrated in *thermal establishments*, using thermal water; and the remaining 7–8 integrated in *thalassotherapy establishments*, using seawater.

A modern spa is typically understood as an establishment that integrates a broad spectrum of professionally managed (therapeutic, wellness, and cosmetic) treatments and services (including fitness and nutrition). This is the concept and perspective of the *International Spa Association* (*ISPA*), which has members in more than 53 (fifty-three) countries.

Portugal has a total coastline estimated at 1792 km, including the coastline of mainland of Portugal and the coastline of the islands of the archipelagos of Madeira and the Azores, 832 km in the mainland and 960 km in the whole of of the islands. The mainland alone, along the seashore has a significant number of population aggregates of varied size, and the excellent climate, landscape, and accessibility gathers privileged conditions for the installation of thalassotherapy establishments, in number that could be much higher than the actual number of existing Thalasso Centres (Gameiro 2011).

What Portugal hopes in the short term is to be able to assert itself as a geographically unique maritime power, because in addition to the so-called territorial sea that extends to the physical limit of 12 nautical miles, the EEZ (exclusive economic zone) could further extend this limit (the proposed extension of the Portuguese continental shelf is awaiting approval by the "Commission on the Limits of the Continental Shelf of the United Nations"). In this way the country should be a good example of involvement regarding the investigation and use of the sea resources.

Viegas Fernandes and Viegas Fernandes (2011) report that there are countries where thalassotherapy is very widespread and practiced in *thalassotherapy centers* or *thalasso centers* and in *thalassotherapy spas*, the latter preferably installed in hotel units. Regarding *thalasso centers*, the numbers are as follows: France, 60; Spain, 57; Tunisia, 40; Italy, 27; Turkey, 12; and United States, 10.

Thalassotherapy benefits for human health are attributed to minerals, either dissolved in seawater or participating in the composition of sea-derived products, such as mud, sand, salt, and marine aerosol. The therapeutic uses of sea-derived mud and sand, called *mudtherapy* and *psammotherapy*, respectively, have already been presented in Chaps. 7 and 14.

Sea salt also has therapeutic interest. The so-called halotherapy is the therapy that uses halo, a word derived from the Greek that means salt.

In the *spa* where *halotherapy* is practiced, the treatment lasts about 40 min and takes place in a room with floor, walls, and ceiling coated with salt, having a vaporizer of humid air that releases about 30 mg/hour of aerosol of salt.

The *spa* where *halotherapy* is practiced must comply with the norms and protocols prescribed in the European Directive CE93/42EEC.

In Portugal there are four *halotherapy centers* located in the cities of Porto, Lisbon, Castelo Branco, and Aveiro.

The experience of miners from the salt mines (derived from seawater) has highlighted the benefits of breathing saline aerosols formed in the natural environment of the mines relative to respiratory diseases such as asthma, bronchitis, rhinitis, and others allergies.

The Wieliczka Royal Mine, located near the city of Krakow in Poland, is an artificial underground structure, which began its construction in 1290 and closed in 2007, which is part of UNESCO's Natural and Cultural Heritage, and has already housed a sanatorium for the sick who suffered from respiratory diseases. Inside the mine the galleries are so spacious that they house a cathedral built with blocks of salt and sculptures equally constructed with salt. From the Royal Mine of Wieliczka, salt blocks are marketed, and they have cavities in their interiors where electric lamps are adapted, that is, electric lamps. The heat released from the lamp causes the formation of a saline aerosol that causes the ambient air to be rich in the ions present in the salt, such as Na^+, K^+, Mg^{2+}, Cl^-, Br^-, and I^-. The salt can also be used in the composition of body scrubs for skin exfoliation treatments, in that they remove dead cells and improve blood circulation.

In turn, *hydrohalotherapy* involves treatments with salt water. This is what happens, for example, in Salies-de-Béarn, southwest of France, where there is a *spa* used by people suffering from psoriasis, a skin disease that affects the elbows and legs, and becomes manifested by the rapid growth and renewal of skin cells. Patients are treated with natural salt water (sea water) baths.

The therapeutic properties of the Dead Sea's hypersaline water in skin diseases have been known since antiquity. A similar situation occurs with the thermal saline baths in Bad Bentheim, Germany, and in the "Blue Lagoon" in Iceland.

A brief note is relative to the so-called *spas salícolas* which are appearing in Portugal, as happens in Castro Marim and in Aveiro (Fig. 16.4), where *hydrohalotherapy* and *hydrohalotherapy* + *mudtherapy* are practiced in local disactivated salt pans.

The *hydrohalotherapy* involves the use of baths in hypersaline seawater, and the *hydrohalotherapy* + *mudtherapy* involves the use of baths in hypersaline seawater and the topical application of dark-colored organic matter-rich saline mud which

Fig. 16.4 (**a**) *Hydrohalotherapy* and (**b**) *hydrohalotherapy* + *mudtherapy* praticed in the *salícole spa* Cale do Oiro, Aveiro

accumulated at the bottom of disactivated salt pans. The organic matter results from the rottenness of the algae formed in the salt pans or tanks. The movements made by the users during the baths can cause mud to be raised from the bottom, which can be swallowed by being suspended. Skin absorption or ingestion, in the event that the sludge may be contaminated with potentially toxic pathogenic microorganisms and/or heavy metals, may pose a health risk to users.

The positive effects of salt water on psoriasis are known, but the agents to which the benefits owe are not yet well elucidated. But there are investigations that point to a biogeochemical contribution because there is evidence of increased levels of certain minerals in the blood serum of patients treated with saline water for four weeks that existed in salt water, such as bromine, iodine, calcium, magnesium, and zinc.

In Portugal there are several active salt-works, located in Aveiro, Figueira da Foz, Samouco, Olhão, and Castro Marim.

Seawater used in thalasso centers is procured and extracted as three modes: boreholes in littoral zones, a set of pipes from the sea bottom, and directly from the sea. In any case the extracted water will undergo purification.

Thalassotherapy takes for granted the use of seawater endowed with all its potential therapeutic properties. Both captation and filtration should not eliminate plankton and should be assured that the captation site is free from pollution.

According to Viegas Fernandes and Viegas Fernandes (2011), the seawater must be used less than 48 h after the capture, and, if it is heated, the temperature should not be higher than 50 °C, in order to avoid the risk of altering its chemistry. The recommended temperatures are between 31 and 35 °C.

Thalassotherapy treatments are indicated mainly for diseases of the respiratory system (asthma, rhinitis, and sinusitis), allergic skin diseases (eczema, acne, and psoriasis), rheumatic diseases, and skeletal muscle diseases (arthrosis, arthritis, sciatica, posttraumatic). Thalassotherapy treatments are contraindicated in the following cases: severe heart failure, very high hypertension, phlebitis, ulcerated or infected inflammatory dermal lesions, and neoplasias. Any thalassotherapic treatment requires previous medical examination, and some persons due to their specific health states, bearing, for instance, contagious diseases, should not have access to treatment. All thalassotherapic treatments should have a medical prescription issued by a medical doctor with competence for that, reporting the clinical state of the patient and the prescribed treatments, acquainted with treatment indications, contraindications, and precautions.

Thalassotherapic treatments are classified into 4 (four) groups:

1. Outdoor treatment – Aerotherapy (baths of iodine-rich air and aerosol)
2. Dry treatment – Cinesitherapy and massotherapy
3. Wet treatment or hydrotherapy treatment – Hydromassage tube, Scottish hydromassage tube, shower massage *Vichy*, Scottish shower, and *jacuzzi*
4. Complementary treatment – specific diets based on fish, shellfish, and algae

According to Gomes et al. (2019) in *thalasso centers*, a rigorous chemical and hygio-sanitary control is required. Parameters such as pH and salinity and the bacteriological analysis of the water from swimming pools and jacuzzis under the control of health authorities should be daily assessed, and the water should be disinfected preferably using ultraviolet radiation. Thalassotherapy presupposes the use of seawater with all its potential therapeutic properties. Capturing and filtration should not eliminate plankton, and it must be ensured that the site of captation is free of pollution.

For Gomes et al. (2019), the main thalassotherapy health indications are diseases of the respiratory tract (asthma, rhinitis, and sinusitis); allergic skin diseases (eczema, acne, urticaria, ichthyosis, and psoriasis); chronic rheumatism diseases (arthritis, arthrosis, and neuritis); inflammatory rheumatism; sciatica; treatment of reeducation in sequelae, bone fractures, and inflammations; osteoporosis; osteoarticular and lymph node diseases; cellulitis; anemia; gynecological diseases (metritis, salpingitis, and vaginitis); fatigue, stress, and depression; chronic or inflammatory gastritis; disorders of the duodenum and small intestine; premature aging; weight loss; rickets; and oral hygiene, teeth and gums.

The main thalassotherapy health contraindications are cancer in the acute or severe phase; evolutionary pulmonary tuberculosis; acute kidney and urinary tract disorders; heart failure and heart disease; very high hypertension; severe hepatic insufficiency; phlebitis; diabetes with malnutrition; inflammatory, ulcerated, or infected dermatological lesions; hyperthyroidism; postpartum and menstruating women, risk of uterine infection; and children who are scrofulous, lymphatic, rickety, and with infected lymph nodes.

16.5 Thalasso Centers: Legislation, Accreditation, and Certification

In *thalasso centers* a rigorous chemical and hygienic-sanitary control should be daily carried out, particularly in the seawater from swimming pools and *jacuzzis*, assessing pH, salinity, and the bacteriological state, the control being granted by the health authorities. Seawater, the essential raw material, is warmed up at 31–35 °C and should be disinfected using the action of ultraviolet radiation and frequently renewed.

In Portugal, deplorably there is not specific legislation in the field of thalassotherapy. France, Tunisia, and Spain are examples of countries that have developed and created specific legislations for thalassotherapy. As a matter of fact, France, actually with about 60 (sixty) *thalassotherapy centers*, was the pioneer country of scientific thalassotherapy; one norm from the Health Ministry dated in 1961 and reviewed in 1971 established the legal conditions needed for opening *thalassotherapy centers*, requisites that should be accomplished.

In Spain, Law no 55/1997 of July 11 established specific legislation that rules, in particular, the sanitary conditions prevailing in the balnearies of thermal spas and of thalassotherapy spas too, where thermal water baths and peloids are applied.

Article no 1 of Law no 55/1997 mentions: "The mandatory compliance with the rules that regulate the hygienic-sanitary conditions of spas and other establishments where thermal baths and thalassotherapy baths are practiced, as well as establishments and facilities where healing mud/peloid are also applied."

Article no 2 of Law no 55/1997 establishes the definitions of: Thermal water, thalassotherapy, balneary, peloid, and establishments where peloids are applied for therapeutic purposes. Peloids are defined as "The products formed by the blend of mineral water (seawater or salt water lake) with a solid component derived from geologic or biologic processes that in natural state or after undergoing previous adequate preparation is topically utilized for therapeutic or aesthetic purposes.

Article no 4 of Law no 55/1997 mentions: "The establishments of thalossotherapy and peloids with therapeutic purposes should have a medical practitioner who is responsible for such treatments."

Article no 7 of Law no 55/1997 establishes: "Those establishments that use peloids with aesthetic purposes will not be able to advertise their possible therapeutic properties."

Finally, Article no 27 of Law no 55/1997 considers: "The owners of the facilities of spas, termal baths and establishments of thalassotherapy and peloids apllication must carry out periodic microbiological controls in those places with the frequency and parameters indicated by the General Directorate of Health."

In the Murcia region of Spain, in the lagoon known as Mar Menor, more precisely in Lo Pagán, San Pedro del Pinatar, there is a quite significant number of balnearies where thalassotherapy is practiced. The lagoon's saline water, sodium chloride-rich water, also rich in Ca and Mg, is characterized by a solid residue estimated at 72366 mg, at 180 °C, and covers an area of 135km^2 and 6 m of maximum water depth. Yet in Spain, on 8 March, 2004, the "Sociedad Española de Talasoterapia" was created, the main goal of which is to supervise the minimum requisites, sanitary safety included, that *thalasso centers* should accomplish, and on top of the requisites is the existence of a physician specialist in hydrology on the directive board.

In 2013, "Le Syndicat National de Thalassothérapie" a sollicité l' AFNOR un "Cadre Legal et Médical de la Thalassothérapie," and as a consequence of that, in 2015, the Norm XP 50–844, "Thalassothérapie-Exigences Relatives à la Prestation de Services," proposes a list of requisites in terms of quality and safety of facilities, equipment, and hygiene, looking at the improvement and harmonization of all *thalassotherapy* services and practices.

In Tunisia, bill no 92–1297 of July 13, modified and updated by the bill no 2001–1081, defines norms and requisites for the activities held in thalassotherapy centers. Tunisia with about 60 (sixty) *thalasso centers* holds the second place among the world's top thalassotherapy destinations. Presently Tunisian *thalasso centers* are following the recommendations proposed by ISO 17680, Tourism and Related Services/Thalassotherapy/Services Requirements, published in 2015, which establishes the requirements for the provision of quality services in thalasso centers, the standard being particularly focused on hygiene and safety.

ISO 17680 focuses on five main pillars:

1. Quality of the infrastructures, such as reception, treatment rooms, and technical areas
2. Facilities and equipments
3. Human resources with the necessary qualifications and being properly trained
4. Best practices, methods, and medical treatments
5. Transportation, storage, and handling of raw materials used in the treatments of seawater, mud, sand, and algae

Besides the referred to conditions, it is understood that all national legal obligations, especially regarding hygiene, health, consumer, and employee rights, are to be fulfilled by the *Thalassotherapy centers*.

Viegas Fernandes and Viegas Fernandes (2011) consider that all *thalassotherapy centers* existing in all countries around the world should be accredited and certified, and mention that since 1996 the "Federation Internacional de Thalassothérapie Mer et Santé" in cooperation with the certifying entity "French Committee for Accreditation and Certification (COFRAC)" confers the accreditation and certification to *thalassotherapy centers* in all countries through the issuance of certificates of quality, *Qualicert*.

Qualicert is an independent entity for certification created in France, in 1991, within the framework of the "Société Générale de Surveillance," and has been considered so far as the first worldwide organization for quality control, inspection, and audit for *thalasso centers*. *Qualicert* certificates warrant the quality of both treatments and facilities applied and existing in *thalasso centers*, and the certificate attribution requires the accomplishment of 7 (seven) fundamental requisites, all contemplated in French and Tunisian legislations (*In*: Viegas Fernandes and Viegas Fernandes 2011):

1. Location in a privileged site nearby the sea
2. Utilization of natural seawater
3. Utilization of natural products extracted from the sea
4. Permanent medical surveillance
5. Constitution of a permanent healthcare professional team
6. Reception service with information about the thalasso center
7. Permanent control of hygiene, safety, and satisfaction degree of clients

The authors of the present book are very much hoping that soon the existing *thalasso centers* in Portugal could follow a specific national regulation in the likeness of the international regulations aforementioned in order to be certified and accredited, fundamental requisites to attract clients.

16.6 Physicochemical and Microbiological Properties of Seawater

Thalassotherapy is encompassed into the scientific and technical field of *medical hydrology*, a competence within the broad field of medicine. Hence only physicians, preferably those having that specialization, should be in charge of the *spas* where thalassotherapy is practiced, and they should be involved as well in the checkup of patients' health state (considering contraindications), prescription, and supervision of the treatment application methods.

Sanitary safety and control, either microbiological or geochemical, due to eventual pathogenicity and toxicity existing in the employed healing sea products are important requirements. Potentially toxic elements, heavy metals included, and potentially pathogenic microorganisms, bacteria and fungi, could be present in such products. In the case of *healing mud/peloid*, consider that their sanitary safety is a fundamental prerequisite to ensure compliance with the general medical and pharmaceutical legal regulations in force. On this subject no specific legislation exists for *healing muds/peloids*, and the same happens for healing sands.

In the European Union, for instance, there are no uniform rules for the microbiological specifications of healing muds/peloids, despite the concern shown by the European Spas Association (ESA).

Thalassotherapy presupposes the use of seawater with all its potential therapeutic properties. Capturing and filtration should not eliminate plankton, and it must be ensured that the site of captation is free of pollution.

Table 16.1 shows the microbiological limits proposed by the ESPA (European Spas Association) for seawater used in thalassotherapy

16.7 Marine Products Utilized in Thalassotherapy and Thalassotherapic Techniques: Hydrotherapy, Algotherapy, Psammotherapy, Pelotherapy, and Climatotherapy

16.7.1 Seawater: Hydrotherapy and Hydropony

The chemical composition of seawater is almost identical to the chemical composition of human plasma or human blood serum, although seawater has a saline concentration three times that of plasma, about 32 g/L in seawater and about 9 g/L in plasma. Thus, if a given volume of seawater is added to a double volume of distilled water, the resulting total volume will have mineral concentration near or isotonic to that of the blood serum. The so-called quinton plasma is formed in the same way, although the seawater used is sterilized. Isotonized seawater can replace blood plasma and cure or ameliorate certain conditions.

Table 16.1 Microbiological parameters proposed by ESPA for seawater used in thalassotherapy

Seawater use	Germs	Limits
Extraction point	Total coliforms	< = 500/100 ml
	E. coli	< = 100/100 ml
	Fecal streptococci	< = 100/100 ml
	Salmonella	0/1 L
	Enteroviruses	0/10 L
Baths/tub	Colony count at 20 °C (after 44 ± 4 h (max.100/ml)	100/ml
	Colony count at 37 °C (after 20 ± 4 h (max. 100/ml	100/ml
	Total coliforms	< = 50/100 ml
	E. coli	< = 10/100 ml
	Fecal streptococci	< = 10/ml
	Staphylococcus aureus	0/10 ml
	Pseudomonas aeruginosa	0/100 ml
Drinking	Colony count at 20 °C (after 44 ± 4 h (max.100/ml)	100/ml
	Colony count at 37 °C (after 20 ± 4 h (max. 100/ml	100/ml
	Total coliforms	0/100 ml
	E. coli	0/100 ml
	Fecal streptococci	0/100 ml
	Pseudomonas aeruginosa	0/100 ml
Inhalation/irrigation	Colony count at 20 °C (after 44 ± 4 h (max.100/ml)	0/ml
	Colony count at 37 °C (after 20 ± 4 h (max. 100/ml	0/ml
	Total coliforms	0/100 ml
	E. coli	0/100 ml
	Fecal streptococci	0/100 ml
	Pseudomonas aeruginosa	0/100 ml

Pros (1980) stated that seawater is the most mineral-rich among all mineral waters because it contains all 92 (ninety-two) natural chemical elements, elements that are incorporated through the skin by osmosis or inhalation of aerosols. In the case of osmosis, the contact of the skin with water lasts for 15–20 min. Osmotic changes are favored if the seawater temperature is close to the normal human body temperature (35–37 °C). According to Tréguer (2003), the treatments should last 2–3 weeks.

The effectiveness of thalassotherapy is higher whenever both salinity and temperature of the water are higher. Filtered seawater, diluted with distilled water (up to isotonic concentration) and sterilized, can be ingested.

16.7.2 Seaweeds: Algotherapy

There are thousands of algae distributed among the following four (4) systematic groups: brown algae (*feofíceas*), red algae (*rutafíceas*), blue algae (cyanophytes), and green algae (chlorophytes).

Worldwide algae production is about eight million tons, part of which is destined for food consumption and part for the manufacture of gelling products, thickeners, and stabilizers (agar, alginates) used mainly in the food, pharmaceutical, and cosmetic industries (Chaussade 2002).

Algae integrate the Chinese pharmacology from 600 B.C. (Hoareau 2002). The algae most commonly used in therapy are as follows: *Fucus vesiculosus* (brown algae), *laminaria* (brown algae), *Lithothamnium calcareum* (red algae), *spirulina* (blue algae), and *Ulva lactuca*.

In France, the *thalassotherapy centers* mainly use brown seaweed, such as *Fucus vesiculosus* and *laminarias*. The algae are harvested live in places free of pollution, then washed and cleaned, and then subjected to a cold microgrinding process called "cryogrinding." Fresh and lyophilized algae are also used.

Algae used in food have the advantages of being rich in fiber and minerals and low in lipids. Cultured and frozen cyanophyte thermal algae, thermal natural mineral water, and fine sediment (mud) deposited on the banks of the Adour are basic constituents of the Terdax peloid, Dax peloid, produced (about 2500 tons/year) and used (60,000 users per year) in Dax, a renowned French spa with a vocation for the treatment of rheumatic and musculoskeletal disorders. Dax peloid also contains special sulfur cycle thermal bacteria that convert sulfate from mineral water into sulfides (Coudron and Counilh 2017).

The study and use of microalgae as a therapeutic resource is very recent, justified by the demand for natural product differentiators in thalasso centers and spas. A group of researchers from the Department of Applied Physics of the University of Vigo, Spain, has been developing microalgae to incorporate them into peloids, both for therapeutic and cosmetic use.

The recent work by Cortés et al. (2017) presents the first results of the project "Production of thermal pellets for use in balneotherapy" developed in Balneario El Raposo, Badajoz, Spain. There were microalgae produced in photobioreactors and, by centrifugation, were concentrated as a paste and characterized by their content of amino acids, carotenoids, fatty acids, and antioxidants. The obtained paste is added to the natural mud or peloid which occurs near the spa and, being maturated in a controlled manner, produces the peloid itself or peloid, applied, for example, in the treatment of osteoarthritis (AO) in El Raposo spa resort (Piles et al. 2017; Rincón et al. 2017). Those peloids that incorporate algae can be used for therapeutic and cosmetic purposes.

At the University of Vigo, Gómez et al. (2017) studied peloids in which brown algae *Fucus vesiculosus* is incorporated, and in other studies other types of seaweed, source of vitamins, proteins, pigments, and minerals, are being used.

Mourelle et al. (2016) state that the use of microalgae can become an important area of development in thermal resorts or spas and in thalassotherapy centers or spas, since marine microalgae, in particular, are important sources of vitamins, pigments, proteins, and other substances that could be suitable for skin care so that they could be used in the treatment of some dermatological diseases such as psoriasis and acne and also for cellulite, dry skin, etc. The authors, considering the possibilities of the use of *microalgae* in peloids to be applied in health resort medicine spas and thalassotherapy spas, have carried out experimental work aiming to compare the thermophysical properties and evaluate skin parameters, such as hydration, elasticity, and fatigue, of different peloids made of microalgae and seawater.

Martin et al. (2017) have investigated mixtures of seawater, bentonite, and microalgae (*Tetraselmis suecica*, *Phaeodactylum tricornutum*, *Nannochloropsis gaditana*, and *Isochrysis galbana*).

Mourelle (2018) published an interesting article entitled "Microalgae and Marine Cyanobacteria En Cosmetica y Thalasoterapia," extracted from an excellent article review entitled "The potential use of Marine Microalgae and Cyanobacteria in Cosmetics and Talassotherapy" produced by Mourelle et al. (2017). The authors begin by distinguishing microalgae from cyanobacteria, both microscopic freshwater and saline organisms, which are very interesting for products of high added value that can be extracted and commercialized: pigments, proteins, essential fatty acids, minerals, and vitamins, with interest in the preparation of natural products, both in the field of food and in the field of cosmetics.

The *cyanobacteria*, which have been called *blue algae*, are prokaryotes capable of performing oxygenic photosynthesis, with the *Spirulina*, *Nostoc*, and *Aphanizomenon* species being the most studied and the most commercialized components, carotenoids, chlorophylls, phycocyanins, amino acids, and minerals.

Macroalgae or any other natural products, e.g., herbs, have been used for decades in thalassotherapy spas as additives in peloids to be applied on the body in the form of poultices or cataplasms.

Mourelle (2018) presents the developments of the investigations carried out and examples on microalgae and cyanobacteria in health (extraction of bioactive components of pharmacological use for the treatment of diseases such as diabetes, hypertension, and alterations of metabolism and immune system), cosmetics, and thalassotherapy. According to the authors, in the Department of Applied Physics of the University of Vigo, Spain, a pilot experiment is underway for the cultivation of marine microalgae in seawater from the Talaso Atlántico Talasoterapia Center in Pontevedra, Spain, and its applications in *thalassotherapy* through the development of products with applications in wellness programs: a bath of microalgae belonging to the species *Nannochloropsis gaditana* cultivated in controlled conditions (temperature, light, CO_2, pH) in a bioreactor and a peloid made from the mixture of the microalgae referred to with a special clay, more precisely a commercial bentonite supplied by Bentonitas Especiales S.A., previously analyzed and discussed (Casás et al. 2011; Casás et al. 2013), and with seawater.

Microalgae are photosynthetic prokaryotic microorganisms (cases of *Cyanophyta* and *Prochlorophyta*) and eukaryotic microrganisms (cases of *Chlorophyta*, *Rhodophyta*, *Phaeophyta*, *Bacillariophyta*, and *Chrysophyta*), and they can grow in fresh water, or in weakly saline water, or yet in highly saline water.

Sea Sand: Arenotherapy or Psammotherapy

This theme is dealt with in Chap. 12 of this same book.

Sea Mud: Mudtherapy and Pelotherapy

The subject involving historical information, concepts, characterization, classification, therapy, and mechanisms of action of healing muds and peloids has already been dealt with in general terms in Chap. 7 of this same book. But it is only healing mud/peloid whose solid phases are formed by sediments deposited in sea or salt lake environments, current or fossil, that is of interest in *thalassotherapy*.

In Portugal there are saline mud used in a traditional and empirical way in or near the following sites of the Portuguese coast, Consolação Beach, Parede Beach, and Meco Beach, where they occur and which have already been mentioned in Chap. 6 of this book. There are still cases of the Dead Sea curative peloid/mud in Israel/Jordan; the Mar Menor, Murcia, Spain; and in the Mar Chiquita, Cordoba, Argentina, locally used for therapeutic and cosmetic purposes.

Recently, involving the three natural ecosystems referred to, have published an excellent and comprehensive article on "Composition and Properties of muds, waters and salts from saline lagoons and lakes used for therapeutic and cosmetic purposes."

The Dead Sea healing mud/peloid, whose water is characterized by having 345 g/L of salt (Katz et al. 2012), is the most recognized in the world, being used in their natural state or participating in formulations in the treatment of dermal and aesthetic affections, and have deserved diverse dissemination (Halvey et al. 1997; Shani et al. 1997; Portugal-Cohen et al. 2009). The Dead Sea really is a therapeutic spa at open air. The therapeutic and cosmetic properties of Dead Sea water and mud are internationally recognized, for instance, to heal *psoriasis*.

The markets of Dead Sea products are extensive and very sound. In 2015 the value of such markets was estimated at about 1 (one) billion of US dollars, a value that is expected to increase to about 3 (three) billion dollars in 2024. The USA is the greatest client, responsible for 35% of the profits of the industry, followed by China.

Actual exportations of both therapeutic and cosmetic mud go to nearly 50 countries. However, without connection to the ocean of the Dead Sea, the increasing water consumption, in Israel, Syria, and Jordan, is responsible for the significantly less water affluence and for the loss of water mass and the consequent retreat of the margins that is actually estimated at 1 m/year. If nothing would be done to counteract the referred to process, by 2050 the Dead Sea could be exhausted. The stabilization of the Dead Sea water mass would involve a plan designed and financed by Israel/Jordan that comprises the construction of desalinization plants in the Red Sea and a water pumping system direct to the Dead Sea.

The ecosystem of the Mar Menor curative mud/peloid, whose water is characterized by having 93 g/L of salt (Carretero et al. 2010), is similar to the Mar Chiquita curative/peloid ecosystem whose water is characterized by 70 g/L salt (Setti et al. 2011).

De Michele et al. (2008) report the local and systemic therapeutic benefits of curative mud or fango, saline and nonsaline muds from various sources, as evidenced in studies conducted by them and other authors in the last 10 years. Saline mud would act "in situ" and at a distance through chemical mediators. Also, the authors highlight the bactericidal activity of some hypersaline muds, as with the Dead Sea mud.

Saline mud from salt pans is also of interest in thalassotherapy. These are examples of saline muds from Slovenia's Adriatic coast, more precisely from Sečovlje Salina Nature Park, which have been used for more than 100 years in "health resorts"/ "thalasso Resorts," including the Thalasso Spa Lepa Vida (Kovač et al. 2017).

In Portugal, some geophysical, geochemical, and microbiological studies have also been carried out in the saline mud of the "Paraíso Salt Park" located in Aveiro, in the Vouga River estuary, in order to understand the saline mud potential for therapeutic and cosmetic applications (Cardoso Gomes 2015).

What has been discussed in this chapter is limited to naturally occurring saline muds/peloids originating in the sea, inland seas, estuaries, lagoons, or salt lakes. However, artificial (or artificialized) saline muds prepared at the time of use or by a maturation process should also be considered after mixing a solid phase (usually bentonite, kaolin, or fibrous clay) with seawater (as a rule hypertonic or isotonic water, Quinton, both of known chemistry and suplied by Quinton Labs, or better Laboratoires Quinton International, SL).

It is the artificial (or artificialized) mud or peloid whose liquid phase involves seawater, the most used for therapeutic purposes in thalassotherapy centers or not, being examples of their current interest, in the former case, the very recent work of Barra et al. (2017) and Seoane et al. (2017) and, in the second case, the work of Silva et al. (2015).

16.7.3 Climate and Maritime Air: Climatotherapy and Aerotherapy

The climate of the marine ecosystems, in the continental areas and even more in the insular areas (oceanic climate), has its own specificities: air purity, thermal stability (low thermal amplitude), hygrometric stability (slightly variable air humidity), high barometric pressure, light and diffuse light, solar radiation, permanent agitation and renewal of air, and high ionization.

The air near the sea, particularly in the surf zone, is rich in aerosols with salts and trace elements in suspension and is renewed in oxygen.

An interesting natural resource of Porto Santo Island is the mild oceanic climate that prevails in the island all year round as well as the characteristic fragrance of marine aerosol. The particular climate features and their health benefits of *climatotherapy* have been studied and reported (Gomes and Silva 2012). However, much more investigation on the health effects of local climatotherapy is needed.

The Dead Sea is a paradigm of natural climatotherapy. The Dead Sea, the highest saline lake on Earth, but the lowest topographically located at 420 m below sea level, has been proven both highly effective and almost without side effects, for skin and joint diseases (Moses 2012; Harari 2012a, 2012b; Dramsdahl 2012).

16.7.4 Indications and Contraindications of the Thalassotherapy Treatments

According to Viegas Fernandes and Viegas Fernandes (2011), the main indications of the treatments of thalassotherapy are as follows: diseases of the respiratory tract (asthma, rhinitis, and sinusitis); allergic skin diseases (eczema, acne, urticaria, ichthyosis, psoriasis); chronic rheumatism (arthritis, arthrosis, neuritis); inflammatory rheumatism; sciatica; treatment of reeducation in sequelae, bone fractures, and inflammations; osteoporosis; osteoarticular and lymph node diseases; cellulitis; anemia; gynecological diseases (metritis, salpingitis, vaginitis); fatigue, stress, and depression; chronic or inflammatory gastritis; disorders of the duodenum and small intestine; premature aging; weight loss; rickets; and oral hygiene, teeth and gums.

The main contraindications of the treatments of thalassotherapy are as follows: cancer in the acute or severe phase; evolutionary pulmonary tuberculosis; acute kidney and urinary tract disorders; heart failure and heart diseases; very high hypertension; severe hepatic insufficiency; phlebitis; diabetes with malnutrition; inflammatory, ulcerated, or infected dermatological lesions; hyperthyroidism; postpartum and menstruating women, because of risk of uterine infection; children who are scrofulous, lymphatic, rickety, and with infected lymph nodes.

Most of the indications and contraindications referred to are essentially based on experience and not on clinical investigation.

References

Abu-Shakra M, Mayer A, Friger M, Harari M (2014) Dead Sea mud packs for chronic low back pain. Isr Med Assoc J 16:574–577

Alberola J, Coll F (2013) Marine therapy and its healing properties. Curr Aging Sci 6(1):63–75

Barra A, Mato MM, Gómez CP, Mourelle ML, Legido JL (2017) Propiedades termofísicas de mezclas de bentonita com água hipersalina para usos en talassoterapia. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 151–154

Bonsignori F (2011) La Talassoterapia. Cure e benessere alle terme marine e al mare. ETS, Pisa

Burkett L (2007) Medical Tourism: Concerns, benefits, and the Americal Legal Perspective. J Legal Med 28(2):223–245

Cardoso Gomes JH (2015) Propriedades de lamas de salinas de Aveiro tendo em vista aplicações dermoterapêuticas e dermocosméticas. Dissertação de PhD, Universidade de Aveiro

Carretero MI, Pozo M, Martin-Rubí JÁ, Pozo E, Maraver F (2010) Mobility of elements in interaction between artificial sweat and peloids used in Spanish spas. Appl Clay Sci 48:506–515

Casás LM, Legido JL, Pozo M, Mourelle L, Plantier F, Bessieres D (2011) Specific heat of mixtures of bentonitic clay with seawater or distilled water for their use in thermotherapy. Thermochim Acta 524:68–73

Casás LM, Pozo M, Gómez CP, Pozo E, Bessieres D, Plantier F, Legido JL (2013) Thermal behavior of mixtures of bentonitic clay and saline solutions. Appl Clay Sci 72:18–25

Caselles MN (2007) Recetas con algas atlanticas. Edicion Algamar, Pontevedra

Cerrada A (2007) Talasoterapia: Revision de artículos médicos publicados en los últimos 20 años. Hidrol Med 2:151–166

Charlier R, Chainuex MC (2009) The healing sea: a sustainable coastal ocean resource: thalassotherapy. J Coastal Res 25(4):838–856

Chaussade J (2002) Os recursos do mar. Instituto Piaget, Lisboa

Codish S, Abu-Shakra M, Flusser D, Friger M, Sukenik S (2005) Mud compress therapy for the hands of patients with rheumatoid arthritis. Rheumatol Int 25:49–54. https://doi.org/10.1007/s00296-003-0402-4

Connell J (2006) Medical Tourism: Sea, sun, sand and surgery. Tour Manag 27:1093–1100

Cortés G, Cortés I, Gómez CP, Mourelle ML, Legido JL (2017) Experience de innovación del peloide de El Raposo. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 61–62

Coudron F, Counilh P (2017) Le Peloide de Dax. Libro de Resúmenes, V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 23–26

Czarnowicki T, Harari M, Ruzicka T, Ingber A (2011) Dead Sea climatotherapy for vitiligo: a retrospective study of 436 patients. J Eur Acad Dermatol Venereol 25:959–963. https://doi.org/10.1111/j.1468-3083.2010.03903.x

De Andrade SC, de Carvalho RF, Soares AS, de Abreu Freitas RP, de Medeiros Guerra LM, Vilar MJ (2008) Thalassotherapy for Fibromyalgia: A randomized controlled trial comparing aquatic exercises in sea water and water pool. Rheumatol Int 29:147–152. https://doi.org/10.1007/s00296-008-0644-2

De Michele D, Giacomino M, Untura-Filho M, Beldarrein A (2008) Efectos sistémicos de los fangos minerales: revision de la literatura de los últimos 10 anos. Balnea 4:115–122

Deledicque AG (1981) Thalassotherapy in Rheumatology. Revue de Medecine 22(6):2269–2272

Dramsdahl E (2012) Multidisciplinary rehabilitation and climatotherapy for chronic diseases at the Dead Sea. Anales de Hidrologia Médica 5(1):53–63

Duparc-Ricoux S, Monnet P, Fabry R (2004) Thalassotherapy: complementary or competitor of the hydro-mineral cure? Press Therm Clim 141:71–77

Flusser D, Abu-Shakra M, FrigerM CS, Sukenik S (2002) Therapy with mud compresses for knee osteoarthritis: comparison of natural mud preparations with mineral-depleted mud. J Clin Rheumatol 8:197–203. https://doi.org/10.1097/01.RHU.0000022542.38402.A9

Gameiro FIJ (2011) A Oferta de Talassoterapia em Portugal. Dissertação de Mestrado, Escola Superior de Hotelaria e Turismo do Estoril

Gomes CSF, Silva JBP (2012) Ilha do Porto Santo: Estância Balnear de Saúde Natural/Porto Santo Island: Unique Natural Health Resort. Madeira Rochas-Divulgações Científicas e Culturais (editor), Funchal, RAM, 237pp. ISBN: 978-972-99004-4-0

Gomes CSF, Silva JBP, Viegas Fernandes J, Viegas Fernandes FM (2019) Thalassotherapy in Porto Santo Island of the Madeira Archipelago: facts and prospects. Bol Soc Esp Hidrol Méd 34(1):9–33. ISSN: 0214-2813. https://doi.org/10.23853/bsehm.2019.0953

Gómez CP, Fernández C, Mourelle ML (2017) Estudio termofísico de mezclas de Fucus vesiculosus com bentonita y disoluciones salinas para usos en centros de talassoterapia. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 125–127

Halvey S, Giryes H, Friger M, Sukenik S (1997) Dead Sea bath salt for the treatment of psoriasis vulgaris: A double blind controlled study. J Eur Acad Dermatol 9:237–242

Harari M (2012a) Climatotherapy of skin diseases at the Dead Sea: an update. Anales de Hidrologia Médica 5(1):39–51

Harari M (2012b) Beauty is not only Skin Deep: the Dead Sea features and Cosmetics. Anales de Hidrologia Médica 5(1):75–88

Hoareau D (2002) Les thérapies marines. Éditions Dangles, Paris

Hobel P (1985) A saúde pela Talassoterapia. Litexa Portugal, Lisboa

Katz U, Shoenfield Y, Zakin V, Sherer Y, Sukenik S (2012) Scientific evidence of the therapeutic effects of Dead Sea treatments. Semin Arthritis Rheum

Kazandjieva J, Grozdev I, Darlenski R, Tsankov N (2008) Climatotherapy of psoriasis. Clin Dermatol 26(5):477–485

Kopel E, Levi A, Harari M, Ruzicka T, Ingber A (2013) Effect of the Dead Sea climatotherapy for psoriasis on quality of life. Isr Med Assoc J 15:99–102

Kovač N, Šmuc NR, Dolenec M, Glavas N (2017) Secovlje saline mud: Research and practical aspects. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 27–29

Lucchetta MC, Monaco G, ValenziVI RMV, Campanella J, Nocchi S, Mennuni G, Fraioli A (2007) The historical-scientific foundations of thalassotherapy: State of the art. Clin Ter 158:533–541

Lunt N, Smith R, Exworthy M, Green ST, Horsfall P, Mannion R (2011) Medical tourism: treatments, marketsand Health system implication: a scoping review. OECD, Directorate for Employment, Labour and Social Affairs, Paris, 55pp

Maraver F (2000) Talasoterapia. In: Sanchez C (dir.). Técnicas Hidrotermales. Videocinco, Madrid, pp 151–163

Maraver F (2015) Talasoterapia: Conceptos y antecedentes. Proc del Congreso International de Talaso. Salud y Bienestar, Nov 22–25, Baiona, pp 1–7

Maraver F, Michán A, Morer C, Aguilera L (2011) Is thalassotherapy simply a type of climatotherapy? Int J Biometeorol 55:107–108

Martin MC, Costas D, Gómez CP, Mourelle ML, Legido JL (2017) Estudio de la adsorción y floculación de bentonita en presencia de microalgas marinas para preparación de peloides. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 163–165

Miranda EM (2014) Legislación y jurisprudência sobre peloterapia. In: Hernandez Torres A (coordinator) Peloterapia: aplicaciones médicas y cosméticas de fangos termales. Fundación Bílbilis, pp 301–309

Morer C (2016) Talasoterapia. Bol Soc Esp Hidrologia Médica 31:119–146

Morer C, Boestad C, Zuluaga P, Alvarez-Badillo A, Maraver F (2017a) Effects of an intensive thalassotherapy and aquatic therapy program in stroke patients: a pilot study. Rev Neurol 65:249–256

Morer C, Roques C-F, Françon A, Forestier R, Maraver F (2017b) The role of mineral elements and other chemical compounds used in balneology: data from double-blind randomized clinical trials. In: International Journal of Biometeorology, Springer. ISSN 0020-7128, https://doi.org/10.1007/s00484-017-1421-2.D

Moses SW (2012) Health effects of Dead Sea Climatotherapy on patients with heart and lung diseases. Anales de Hidrologia Médica 5(1):11–19

Mourelle ML (2018) Microalgas y Mianobacterias Marinas en Cosmética y Talasoterapia. Tribuna Termal: Turismo de Salud y Bienestar 39:64–68

Mourelle ML, Gómez CP, Legido JL, Legido N (2016) Innovación en el uso de microalgas en termalismo. Bol Soc Esp Hidrol Méd 31:53–64

Mourelle ML, Gómez CP, Legido JL (2017) The potential use of marine microalgae and cyanobacteria in cosmetics and thalassotherapy. Cosmetics 4:46. https://doi.org/10.3390/cosmetics4040046

Munteanu C, Munteanu D (2019) Thalassotherapy today. Balneo Res J 10 (4): 440–444. https://doi.org/10.12680/balneo.2019.278

Piles ST, Burgos BI, Galán IG, Rincón EO (2017) Estudio comparado entre peloides naturales y madurados de forma controlada, de benefícios clínicos en la osteoartritis en el balneário El Raposo. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 63–64

Portugal-Cohen M, Soroka Y, Ma'or Z, Oron M, Zioni T, Menahen F, Neuman R, Kohen R, Milner Y (2009) Protective effects of a cream containind Dead Sea minerals against UVB-induced stress in human skin. Exp Dermatol:1–8

Pros JS (1980) El poder curative del mar (talasoterapia). Editorial Sintes, Barcelona

Rincón EO, Galán IG, Piles ST (2017) Estabilización inmunoneuroendocrina como mecanismo de efectividad de los benefícios de la peloterapia sobre la osteoartritis: Un estúdio en el balneário

"El Raposo". Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 65–67

Rogozian BN, Efimenko NV, Kaĭsinova AS, Babiakin AF (2011) Thalassotherapy for the patients suffering osteoarthrosis. The medical technology. Vopr Kurortol Fizioter Lech Fiz Kult 88:51–54. https://doi.org/10.17116/kurort2011651-54

San José JC (2004) René Quinton : Centenário de "L'eau de mer", milieu organique. Bol Soc Esp Hidrol Med 19(1):17–22

San Martin J (1995) Talasoterapia: Proyección terapêutica actual. Na R Acad Nac Med (Madrid) 112(2):347–379

Schuh A (2009) Die Evidenz der Klima- und Thalassotherapie. Ein Rev Schweiz Z Ganzheitsmed 21:96–104. https://doi.org/10.1159/000287219

Seoane V, Ramos S, Gómez CP, Mourelle ML, Legido JL (2017) Experiências com limos marinos en el Talaso Atlántico. Libro de Resúmenes del V Congreso Iberoamericano de Peloides, Balneario El Raposo, Badajoz, pp 167–169

Setti M, Soria C, Marinoni L, Roca Jalil E, Andrade D, Barbagelata R, Bashini M (2011) Natural materials from Laguna Mar Chiquita and their possible use in human health. 11th International Conference on salt Lakes Research, Laguna Mar Chiquita, Cordoba, Argentina

Shani J, Seidl V, Hristakieva E, Stanimirovic A, Burdo A, Harari M (1997) Indications, contraindications and possible sideeffects of climatotherapy at the Dead sea. Int J Dermatol 36:481–492

Silva JBP, Santos D, Amaral MH, Ramos P, Franco A, Gomes CSF, Lobo JMS (2015) Casos de estudo de tratamento de patologias mamárias com peloide terapêutico. Balnea, 10, 120–122 (editores Maraver F, Vela L, Ankili WL)

Sukenik S, Neumann L, Flusser D, Kleiner-Baumgarten A, Buskila D (1995) Balneotherapy for rheumatoid arthritis at the Dead Sea. Isr J Med Sci 31:210–214

Sukenik S, Flusser D, Abu-Shakra M (1999) The role of spa therapy in various rheumatic diseases. Rheum Dis Clin N Am 25:883–897

Tinghérian C (2005) Guide de la thalasso. Éditions Solar, Paris

Tréguer Y (2003) La Thalassotérapie. Éditions le Cavalier Bleu, Paris

Veillet-Berry M-N (2011) Le bienfait de la thalasso. L'énergie de la mer au service de votre santé et de votre beauté, Marabout Hacette Livre, France

Viegas Fernandes J, Viegas Fernandes FM (2011) Turismo de Saúde e Bem-Estar no Mundo: Ética, Excelência, Segurança e Sustentabilidade. Editora SENAC, São Paulo, Brasil, 264pp

Viegas Fernandes J, Viegas Fernandes FM (2014) Algarve's health and wellness destination. Medical Tourism Magazine, issue 30, January/February 2014, USA

Zijlstra TR, van de Laar MA, Bernelot Moens HJ, Taal E, Zakraoui L, Rasker JJ (2005) Spa treatment for primary fibromyalgia syndrome: a combination of thalassotherapy, exercise and patient education improves symptoms and quality of life. Rheumatology (Oxford) 44:539–546. https://doi.org/10.1093/rheumatology/keh53

Index

C. Gomes, M. Rautureau (eds.), *Minerals* latu sensu *and Human Health*,
https://doi.org/10.1007/978-3-030-65706-2