Hicham Chatoui · Mohamed Merzouki ·
Hanane Moummou · Mounir Tilaoui ·
Nabila Saadaoui · Amina Brhich *Editors*

Nutrition and Human Health

Effects and Environmental Impacts

Springer

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For Morocco,
To everyone in the world
To Professor Nour Eddine ASKOUR
To Professor Jilali EL HAJRI
To our parents
To our wonderful wives and husbands
To our sisters and brothers
To our daughters and sons
To our friends and colleagues
To all the members of our families

To the soul of Prof. Mohamed Najimi.
We have known you as both a reverent colleague and a very cherished friend. You had helped your teammates, students, and the Department of Biology in a myriad of ways to succeed as you had spared no effort to contribute to the field of scientific research in Morocco and worldwide.
For the diverse memories, good and hard times we shared, we say "thank you."
May you rest in peace.

Foreword

As sustainability continues to be a high concern in the scholarly community, food security has become a critical issue. Food supplies are challenged by factors such as toxicity, substandard food processes, difficulties in providing food to struggling populations, and changes to the environment due to climate change. Legislation can protect public health, but lawmakers must understand the current complications facing food security today.

Food security legislations and regulations have long been impacted by a variety of factors including legal issues, nutrition, ecology, and health.

The intent of this book is to:

- Improve and categorize the real and perceived food security and safety issues
- Provide assistance to the reader to have an overview
- Define and describe legislations and international standards of food security
- Define and describe environmental effects on nutrition and human health
- Improve nutrition and health outcomes of vulnerable populations
- Enhance agro-food production systems
- Explore the impacts of climate changes in agriculture
- Exposure assessment of smart food
- Strengthen the institutional capacity to solve problems of food insecurity in sub-Saharan countries.

Food security issues have a significance and high priority in sustainable development goals which are blueprint to achieve a better and more sustainable future for all.

Otherwise, food security is potentially related to climate change impacts on human health, crop productivity, and food availability.

This book is a collection of innovative research that examines food safety issues with regard to international policies as well as sustainable development goals.

Featuring coverage of a broad range of topics including ecotoxicology, smart food, and wastewater impact, this book aims to protect and improve the health of vulnerable populations as well as explore food insecurity in the hope of finding solutions. This book is ideally designed for university students, from undergraduate to PhD level, professors, researchers, professionals, environmentalists, physio-pathologists, medical doctors, epidemiologists, policies makers, and sociologists.

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Our sincere thanks to the Private University of Marrakech (UPM) and to the Sultan Moulay Slimane University of Béni Mellal.

Additionally, none of this would have been possible without the contribution of different parties. We are eternally grateful to the authors of all chapters of our book. We would like to express our deepest appreciation for their seriousness, persistence, and patience during all the steps of the book process.

We also want to acknowledge all our institutions, which have made our professional life such a pleasure.

We gratefully acknowledge the time and expertise devoted to the revision of all the chapters of our book by reviewers, who dedicated their efforts freely to review its different chapters, with attention to the scientific and linguistic aspects.

We should not forget all the scientists and authors of the numerous papers and reviews cited in this book.

Editorial Advisory Board

Contents

Part I
Climate Changes, Agricultural Productions and Environmental Impacts

Climate Change Impact on Agricultural Production in the Sahel Region

Houda Nassah, Lamia Daghor, Hicham Chatoui, Abdessamad Tounsi, Fatima Khoulaid, Younes Fakir, Salah Erraki, and Said Khabba

Abstract The agricultural sector, which is a predominant part of the economy, is facing climate change alternating with water scarcity. The impacts of climate change are presented by extreme and frequent meteorological events that threaten crops and its evolution. Several studies have shown that climate change would have a negative impact on climatic variables (temperature and precipitations) and thereafter the crop and its yield.

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Some of these studies highlighted that annual volume precipitation would tend to decrease while indicating a concentration over time. This situation would explain the increasing frequency of floods and droughts in the Sahel region over the past two decades.

Other studies have indicated that temperatures tend to increase, which will accelerate the evolution and development of the crop cycle. This acceleration can deteriorate the intensity of flowering and lead to yield reductions.

The Sahel zone is identified by GIEC (Le Groupe d'experts intergouvernemental sur l'évolution du climat) experts as one of the most vulnerable regions in the world to climate change. This semiarid region of Africa has seen its temperature rise over the past 60 years, with a transformation of the rainfall patterns. In this chapter, we propose a literature review on the potential effects of climate change on agriculture and livelihoods in Sahelian Africa.

Keywords Climate · Crops · Precipitations · Floods · Drought · Temperature

1 Introduction

All future global climate projections (near and far future) predict an increase in average warming, in addition to precipitation variability and also a greater frequency and intensification of extreme events (GIEC 2014).

The impacts of this climate variability vary from one region to another with particularly significant socioeconomic consequences in developing countries (Sultan 2015; Nangombe et al. 2018). West Africa is one of the most regions that is affected by climate change (Dilley et al. 2005) and (GIEC 2014).

Increasing temperatures, changing rainfall patterns, and increases in frequency of extreme events, such as droughts, storms, floods, and extremes weather, will present important challenges to agriculture.

Several authors (Guichard et al. 2012; Morice et al. 2012; Salack 2013; Faye et al. 2019) had shown that agriculture, which is the economic pillar of the Sahel region, is threatened by the 2 °C temperature increase since 1950 and the high variability of rainfall and the intensification of extreme events.

In this chapter, we propose a literature review that focuses on the impact of climate change on the agricultural sector and its evolution.

2 The Area Most Vulnerable to Climate Change

2.1 Geographical Position

The geographic Sahel is generally defined by the lands located south of the Sahara, intermediate between the Saharan zone (arid) and the Sudanian zone (humid tropical), and roughly situated between 200 and 600 mm isohyets. This geographic area

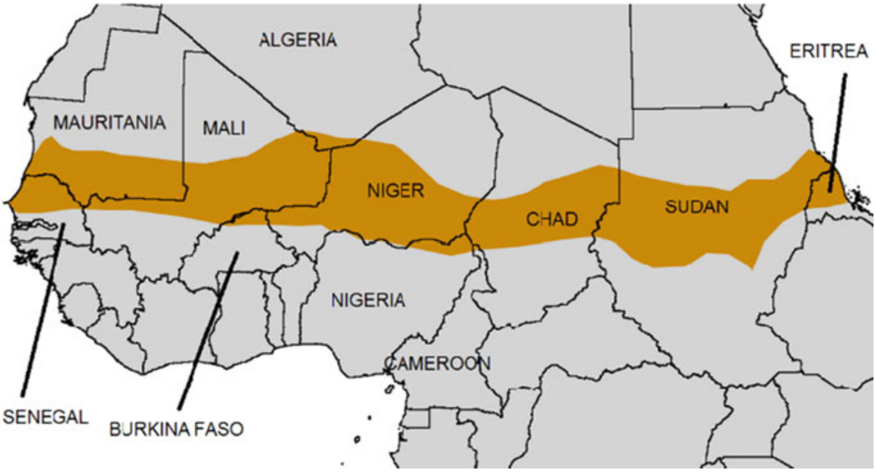

Fig. 1 Location of the Sahelian band

Table 1 Demographic characteristics of the Sahel region

	Senegal	Mali	Burkina	Niger	Chad	Mauritania
Population	11.2	12.8	13.3	13.3	9.9	3.1

covers several countries, located between Senegal (to the west), Sudan (to the east), northern zones of Nigeria, Central African Republic (to the south), and Ethiopia, Eritrea, and Somalia (to the east) (Fig. 1) **(**OCHA 2016**).**

2.2 *Population*

The Sahel had around 64 million inhabitants at the start of the twenty-first century. Five countries are of comparable size, with 10–13 million inhabitants, while Mauritania has about four times less (3 million). In 1950, they had a population of about 17 million people, while in 2015, they were expected to have already 89 million inhabitants. United Nations projections predict 540 million inhabitants by 2100, 66 times more than two centuries ago (WPP 2015).

These demographics as planned will have enormous consequences in many countries, in many areas ranging from agricultural production to prospects for socioeconomic development and political stability (Table 1).

2.3 Climate

The Sahel is characterized by a semiarid climate, hot, with two well-marked seasons: a dry season lasting about 8–9 months, and a rainy season (wintering) of 3–4 months. The climate is not homogeneous inside the Sahel, because there is a strong gradient between the southern zones with the Sudano–Sahelian climate with more abundant rains and the northern zones with the Saharan climate, almost desert. The increase in extreme rainfall events in the Sahel is one of the characteristics of climate change. Researchers of Hydrology and Environment Transfers Study Laboratory (LTHE) have shown that rainfall extremes have become more marked from 1990 onward by working on a set of 43 daily rainfall series available over the period 1950–2010.

A statistical analysis based on the theory of extreme values made it possible to provide a regional vision of the spatial organization of rainfall extremes.

Figure 2 highlights a clear difference in the evolution of total annual precipitation (annual cumulative) and annual daily maximums over the Sahel since 1950. While the annual totals remain largely in deficit compared to the average of the 1950–1970 wet periods, the average of the annual maxima displays values higher than what they were between 1950 and 1970.

The two curves clearly differ from the end of the 1990s. This confirms that a significant change in the rainfall regime occurred at the turn of the century, with the extremes of rainfall becoming more marked.

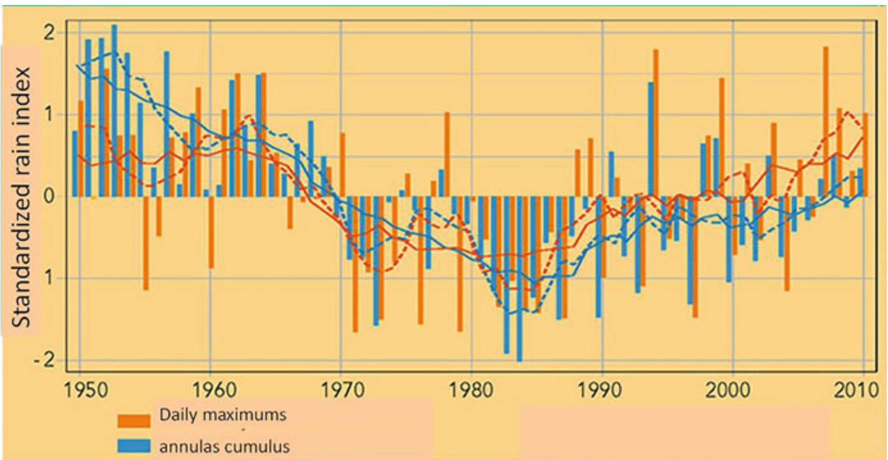

Fig. 2 Comparative evolution of annual totals and maximum rainfall in the Sahel between 1950 and 2010

2.4 Agriculture

The agricultural sector occupies an essential place in national economies, from 16% in Senegal to 48% in Chad (AGRA 2018), and provides most of the jobs: 32% in Senegal; more than 70% in Burkina, Mali, and Chad; and 81% in Niger (Allen et al. 2018). Agriculture is the main economic activity in the region (50% of the regional area). The agricultural sector is characterized by extensive production systems dominated by food crops (rice and maize) and so-called cash crops (groundnut, sesame, watermelon, vegetable, and fruit crops) (Janicot et al. 2015**)**. The major crop remains mainly rain-fed agriculture (Janicot et al. 2015).

3 The Impacts of Climate Change on Agricultural Sector

Understanding the relationship between the agricultural sector and climate change is a challenge for researchers. Several studies have discussed the direct and indirect effect of climate change on agriculture since the 1980s with the work of Callaway (2004), Rosenzweig and Hillel (1995), GIEC (2001, 2007), Tubiello et al. (2007), and Barrios et al. (2008).

In this context, Sultan et al. (2005) mentioned that the various climatic factors related to temperature or precipitation have direct effects on crops and therefore on agricultural yields**.** In this chapter, we will present the impact of temperature increase and precipitation intensification on agricultural production through a bibliographic study.

3.1 The Temperature Rise Impact on Agricultural Production

Temperature is considered to be the most important factor affecting crop phenology (Grab and Craparo 2011). Several researchers estimate that the increase in temperature will be reflected by the modification of phenological development rates and the growth of plant cover. Erez et al. (2000), Adams et al. (2001), Hilaire et al. (2002), Rodrigo and Herrero (2002), Lu et al. (2006), Doi (2007), Legave (2007), Lopez and DeJong (2007), Day et al. (2008), Seguin (2010), Grab and Craparo (2011), and Niezderholzer (2014) have confirmed that high temperatures reduce the development time of the fruits and accelerate their growth, thus advancing the harvest date. A temperature increase of 1 °C leads to an increase in growth phases of about 7 days (Chmielewski and Rötzer 2001).

Several results confirmed that the increase in temperature caused a decrease in yield for tomatoes (Adams et al. 2001), (Garg and Cheema 2011**),** for cereals **(**Porter and Semenov 2005), and for strawberry plant (Ledesma et al. 2008).Recent studies predict, using climate models, an upward trend in temperatures of +2.8 °ecent studies predict, using cl–2060) (Sultan et al. 2013, 2014). The crop models used by Sultan et al. (2013, 2014) predict a decrease in potential yields throughout the Sahel. This effect is mainly due to higher temperatures shortening the crop cycle (Roudier et al. 2011; Sultan et al. 2013).

3.2 The Precipitation Impact on Agricultural Production

The total amount of rainfall during the season is an important factor in the development and production of different crops (Dancette 1980; GIEC 2001, 2007), while climate change would modify rainfall and its frequency (Noor et al. 2018).

Several studies have shown that increased rainfall intensification will generate periods of floods and droughts (Allen and Ingram 2002; Trenberth et al. 2003; Held and Soden 2006).

The rains, as they become more violent, flood, destroy crops (GIEC 2014). These frequent and destructive storms are linked to the warming of neighboring oceans. The phenomenon generates a stronger evaporation than before (GIEC 2014).

Several studies have shown that the occurrence of water stress at the beginning of the crop's growing cycle is damaging to its development and yield (Schilling 2001).

4 Conclusion

The Sahel zone is identified by GIEC (Le Groupe d'experts intergouvernemental sur l'évolution du climat) experts as one of the most vulnerable regions to climate change in the world. The temperature of this region has been rising over the past 60 years, with a transformation in the rainfall pattern. The agriculture sector, which is one of the Sahel band's priority development sectors, will have to face the risks inherent in climate change.

In this chapter, the effects of temperature increase and changes in rainfall cycles on agricultural production are presented through a literature review.

The results of literature research on the impact of climate change on agricultural production indicate global agricultural yield losses of 2% per decade (on average) as a result of increased temperature rates and intensified rainfall.

Researchers are trying to anticipate the consequences of climate fluctuations on agricultural production and yield. They rely on complex models that combine climatic, agronomic, and economic data. This research recommends the development of varieties with greater drought tolerance.

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Bioactive Components from Agrofood Waste: Methods of Delivery in Food Products

Radha Kushwaha, Vinti Singh, Reshma Saroj, Monika Singh, and Devinder Kaur

Abstract Various industrial, agricultural, household, and other food sector food waste/residues are raising concern due to environmental pollution and raise a question regarding agricultural and food safety and security. They can be considered as vital sources of bioactive compounds and nutraceuticals which have a great potential to cure several diseases and disorders found in human. Food and medicines can be used as a vehicle for the delivery of bioactive compounds and micronutrients at suitable levels that provide health benefits. Demonstration of successful and effective incorporation of bioactive compounds into foods is essential for the commercialization of new bioactive ingredients and functional food ingredients. In the next few years, these approaches could provide an innovative approach to increase the production of specific compounds for use as nutraceuticals or as ingredients in the design of functional foods. The development of functional foods can go through the addition of bioactive compounds which can be of either plant or animal origin. Various technologies can be applied to fulfill the requirements, for example, microencapsulation, nanoencapsulation, emulsions coacervation, spray-drying, spray cooling, freeze-drying, fluid-bed coating, extrusion technologies, and edible coatings. They are useful tools to improve the delivery of bioactive compounds like minerals, vitamins, probiotics, prebiotics, lycopene, phytosterols, and antioxidants into the foods. There has been an excellent increment in the number of food products containing bioactive components with health-promoting or disease-preventing effect. In this review, a comprehensive study of various techniques for addition of bioactive components citing successful research work has been discussed. Further, phenolic compounds, probiotics, prebiotics, and antioxidants were reviewed as model bioactive substances to demonstrate their efficient utilization in the development of functional ingredients, nutraceutical products, health benefits, and bioprocesses.. Value addition of food waste resources has also been discussed.

Keywords Bioactive · Functional food · Phenolics · Microencapsulation · Agriculture

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1 Introduction

Agricultural and food industries are major producers of solid and liquid residues with high biochemical concentrations. These wastes and residues can lead to substantial soil, air, and water pollution. These agricultural and industrial solid wastes are discarded in landfills to produce greenhouse gases and may occupy large volumes with slow systematic degradation, especially in countries with very cold climates (Esposito et al. 2020). Contaminated leaching from these dumped by-products can pollute surface and groundwater, making it unsuitable for drinking and other consumption-based applications. Succeeding eutrophication slows down and decreases the growth of aquatic plants and animals, thus having a long-term effect on both the micro and macro ecosystems (Kumar et al. 2017). These by-products are the richest sources of many bioactive components, antioxidants, and fiber contents. Therefore, these by-products and wastes can be valorized to reduce soil, water, and air pollution and lead to value-added products, thus creating subsidiary markets and income sources (Ben-Othman et al. 2020). Bioactive ingredients are pharmacologically and biologically active molecules obtained from natural sources or through chemical synthesis. In the last years, several molecules have been discovered by different methods (supercritical fluid extraction). Bioactive compounds are being used through microencapsulation techniques in various industries such as geomedicine, pharmacology, agrochemicals, plant science, cosmetics, and nanobioscience along with the food industry. Bioactive compounds promoted weight management and lowered the risk of obesity, cardiovascular diseases, and diabetes (Teixeira et al. 2014). The term bioactive is made up of two words: *bio*- and -*active*; *bio* from Greek *bios* means life, and *active* comes from the Latin word *activus*, which means energetic. These are the compounds having biological activity, which has a direct effect on a living organism. These compounds' effects may be positive or negative depending on the substances, the dose, or the bioavailability. *Encyclopedia of Food and Culture* says that the term bioactive compounds is related to nonessential biomolecules that are found in foods and able to alter metabolic processes. They promote better health. Bioactive compounds may be essential or nonessential compounds that occur naturally, are an element of a food chain, and can be shown to affect human health (Biesalski et al. 2009). Bioactive compounds contain substances that are found in very low quantities in plants and some foods like fruits and vegetables, cereals and pulses, nuts, and oilseeds, and they show positive effects on the body that can promote good health. The recent progress in researches related to bioactive compounds attracts the attention of many researchers, and thus, many bioactive compounds had been synthesized from natural sources and chemically. Bioactive compounds can be extracted from both plant and animal products or can be synthetically produced. For example, plant-derived bioactive compounds are tea phenolics, quercetin, carotenoids, lycopene, and polyphenols (from fruits and vegetables); rutin, isoflavones, curcumin, and ellagic acid (pomegranate juice); proanthocyanidin (cranberry juice); podophyllotoxin (mayapple); or polysterols (from oils); and in animal products are fatty acids found in milk and fish, flavonoids, carotenoids, carnitine, choline, coenzyme Q, creatine, polysterols, polyesterogens, glucosinolates, polyphenols, anthocyanins, and prebiotics (Santana-Méridas et al. 2012; Georganas et al. 2020).

This chapter is focused on the uses and different methods of delivery of these agricultural and industrial bioactive compounds into food systems for their value addition.

1.1 Bioactive Components from Agricultural Waste

Agricultural and food industry by-products can be generally classified as (1) plant by-products and their processing wastes and (2) animal processing by-products. Some of the major bioactive compounds found in different agriculture and food waste and residues are given in Table 1. Bioactive compounds extracted from food waste include various vital molecules that can be utilized for the production of several functional foods, food additives, and nutraceuticals (Joana Gil-Chávez et al. 2013). Bioactive phytochemicals like sterols, tocopherols, carotenes, polyphenols, and terpenes extracted from different agrofood by-products contain considerable amounts of antioxidant properties. Therefore, these bioactive components are extracted from such residues/waste by using different extraction techniques, viz., solvent extraction (SE), subcritical water extraction (SCW), and supercritical fluid extraction (SFE), using ultrasounds, enzymes, and microwave techniques to ensure the utilization of agrowaste and food security and safety (Kumar et al. 2017). Consequently, they can be used as natural antioxidants for the production of healthy food and nutraceuticals to enhance their shelf-life (Kalogeropoulos et al. 2012). These bioactive compounds are helpful for the treatment and prevention of a variety of human diseases and to also prevent oxidation and microbial degradation in foods (Fig. 1). These bioactive components powerfully interrelate with DNA, proteins, and other biological molecules of the body to generate positive effects, which can be applied for the production of natural therapeutic and nutraceutical medicines (Ajikumar et al. 2008; Lemes et al. 2016). For the delivery of these bioactive and antioxidant components into food and nutraceutical and pharmaceutical medicines, different techniques have been used in past decades, which will be discussed in detail.

2 Various Techniques for Delivery of Bioactive Compound in Food

Bioactive food compounds are added to the food product by the following techniques: edible coatings, microencapsulation, nanocapsulation, nanoemulsion, liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC).

Table 1 Bioactive components in different industrial food waste residues

Source	Bioactive components	References
Apple (peel and pomace)	Epicatechin, hydroxycinnamates, phloretin, catechins, anthocyanins, quercitin glycosides, procyanidins, chlorogenic acid, glycosides,	Foo and Lu (1999), Wolfe and Liu (2003)
Banana (peel)	Catecholamine, gallocatechin, cyaniding, delphinidin, anthocyanins.	Someya et al. (2002), González-Montelongo et al. (2010)
Carrot (peel)	β-Carotene and polyphenols	Chantaro et al. (2008)
Citrus fruit (peel)	Eriocitrin, hesperidin, narirutin, naringin	Coll et al. (1998)
Tomato (skin and pomace)	Carotenoids and antioxidants (lycopene, β-carotene, Ellagic, chlorogenic acids, rutin, and myricetin)	Strati and Oreopoulou (2011), Puranik et al. (2019) and Kaur et al. (2019)
Guava (skin and seeds)	Catechin, galangin, cyanidin 3-glucoside, kaempferol, gallic acid, homogentisic acid	Deng et al. (2012), Shukla et al. (2018)
Cucumber (peel)	Chlorophyll, phellandrene, pheophytin, caryophyllene.	Zeyada et al. (2008)
Barley (bran)	β-Glucan	Sainvitu et al. (2012)
Mango (seed)	Gallic acid, gallates, ellagic acid, gallotannins, tannins	Arogba (2000), Puravankara et al. (2000)
Potato (peel)	Caffeic acid, gallic acid, vanillic acid.	Zeyada et al. (2008)
Litchi (pericarp and seeds)	Cyanidin-3-glucoside, malvidin-3-glucoside, cyanidin-3-rutonoside, epicatechin-3-gallate, gallic acid	Lee and Wicker (1991), Duan et al. (2007)
Rice (bran and bran oil)	Tocopherols, γ-oryzanol, other phenolics, sterols, triterpene alcohols, 4-methyl-sterols, β-sitosterol, campesterol, stigmasterol, squalene	Oliveira et al. (2012), Maurya and Kushwaha (2019)
Wheat (bran and germs)	Antioxidants and phenolic acids	Wang et al. (2008)
Pomegranate (peel and pericarp)	5-diglucoside, gallic acid, cyanidin-3-diglucoside, cyanidin-3,5-diglucoside, delphinidin-3	Noda et al. (2002), Saroj et al. (2020)
Coffee (spent coffee grounds)	Gallic acid, phenolic compounds, antioxidants	Mussatto et al. (2011), Zuorro and Lavecchia (2012)
Tea (used tea leaves)	Caffeine	Rebecca et al. (2014)
Winery by-products	Procyanidins B1 and B2, gallic acid, peonidin 3-*O*-glucoside, syringic acid, quercetin 3-β-d-glucoside, catechin, epicatechin gallate, delphinidin 3-glucoside, epicatechin, and malvidin 3-glucoside	Melo et al. (2015)
Corn husk	Polyphenols, tannins, flavonoids	Vijayalaxmi et al. (2015)
Melon	Xanthan	López et al. (2004)
Olive	Polyphenols	Lee and Lee (2010)
Peanut husk	Polyphenols, tannins, flavonoids	Vijayalaxmi et al. (2015)
Olive pomace	α-, β-, γ-tocopherol, α-tocotrienol, phenolics content, and antioxidant activity	Nunes et al. (2018)

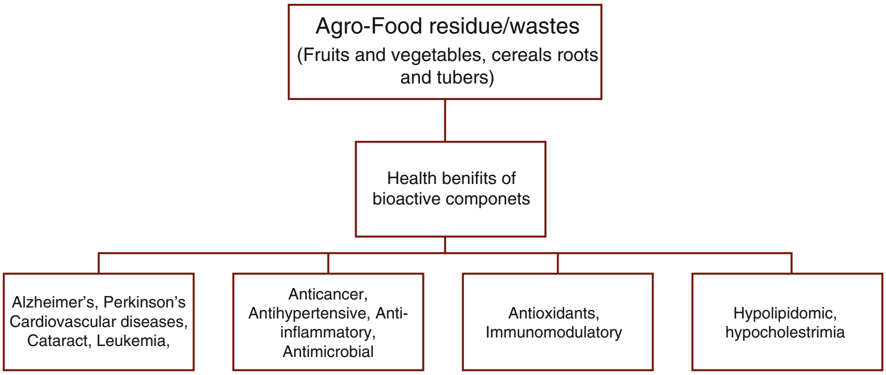

Fig. 1 Bioactive components' extraction and health benefits from different food sources

2.1 Edible Coatings

An edible coating can be defined as a thin layer of edible material applied on the surface of the food that gives a barrier against migration of O2, CO2, moisture, volatile compounds, aroma, fat, and other solutes (Kester and Fennema 1986; Biquet and Labuza 1988; Cuq et al. 1995). Additionally, edible coatings can also be used as encapsulating matrices of bioactive compounds to enhance the quality of food products, supporting the controlled release, which acts on a desired site and time at a specific rate (Pothakamury and Barbosa-Cánovas 1995). It helps not only to enhance the shelf life, reducing the risk of pathogenic microbial growth on food, but also to provide a functional product with health remuneration to the consumers. The inclusion of bioactive compounds into food products offers many advantages in food preservation and helps the development of functional foods. However, these bioactive compounds may adversely affect foods like off-flavors and an early loss of functionality (Ayala-Zavala et al. 2008; Silva-Weiss et al. 2013). Encapsulation with the help of edible coatings is a potential technique that can resolve this problem. Different encapsulation techniques may be used, depending on the nature and purpose of the bioactive compound. For example, (a) incorporation on the external surface of the film, (b) at the interface between the film and the food, (c) among multilayered edible coatings, and (d) dispersed among different sections of the film. According to Quirós-Sauceda et al. (2014), they are divided into two major parts: water-soluble and water-insoluble. Water-soluble compounds are further divided into polysaccharides (methyl celluloses, sodium carboxymethyl cellulose, guar gum carrageen, sodium alginate, chitosan, and gum Arabic) and nonpolysaccharides (ethylcellulose, shellac, waxes, sugar, sorbitan ester, linear fatty acids, etc.).

2.2 Microencapsulation

Microencapsulation (ME) has been defined as the technology of packaging solid, liquid, and gaseous materials in small capsules that release their contents at controlled rates over prolonged periods. It is a process of enclosing micron-size core particles of solids and droplets of liquids or gases in an inert shell. The inert shell in turn isolates and protects the enclosed core materials from the external environment (Ghosh 2006). This outer shell also controls the rate of release of the core contents under the influence of specific environmental conditions (Anal and Singh 2007). Microencapsulation is a phenomenon by which a core material, i.e., bioactive ingredient, is enclosed within a secondary material to form a microcapsule. These secondary materials are called the encapsulant, matrix, or shell. They avoid unwanted interactions between bioactive and food components. It also inhibits the chemical reactions that facilitate degradation of the bioactive ingredients, which shows undesirable changes in flavor and odor and sometimes indicates adverse health effects. Keeping the end use of encapsulated ingredients during encapsulation is crucial. It requires knowledge about the core, the encapsulant materials, interactions among the core, matrix, and the environment, microencapsulated ingredient stability during storage and incorporation into the food matrix, and the process that controls the release of the core. The cores used during microencapsulation are given in Fig. 2. However, information is sometimes lacking in how the core interacts with other food components; it depends on consumption, its active site (de Vos et al. 2006).

2.2.1 Microencapsulation Processes

Microencapsulation processes are used to produce several microencapsulated food ingredients and pharmaceutical products. Microencapsulation is a process in which a material (core), i.e., bioactive or functional ingredient, is packed within a secondary material to form a microcapsule (Fig. 3A). These secondary materials are known as the matrix or encapsulant or shell which forms a protective coating around the core that isolates it from its surrounding environment until its release is triggered by changes in its environment. The shell also controls the rate of release of the core contents under the influence of specific environmental conditions (Anal and Singh 2007). The microencapsulation process has been considered as an excellent use to the food industry, for the production of foods containing functional and nutraceutical ingredients (like probiotics and bioactive components) and controls the release of flavor, polyunsaturated oils, vitamins, and odor. The main reasons for the microencapsulation of materials can be explained as follows (Ghosh 2006; Gharsallaoui et al. 2007; Kuang et al. 2010):

- Protection of unstable, sensitive materials from environmental conditions.
- Controlled, sustained, or timed release of materials.
- Targeted release of materials.

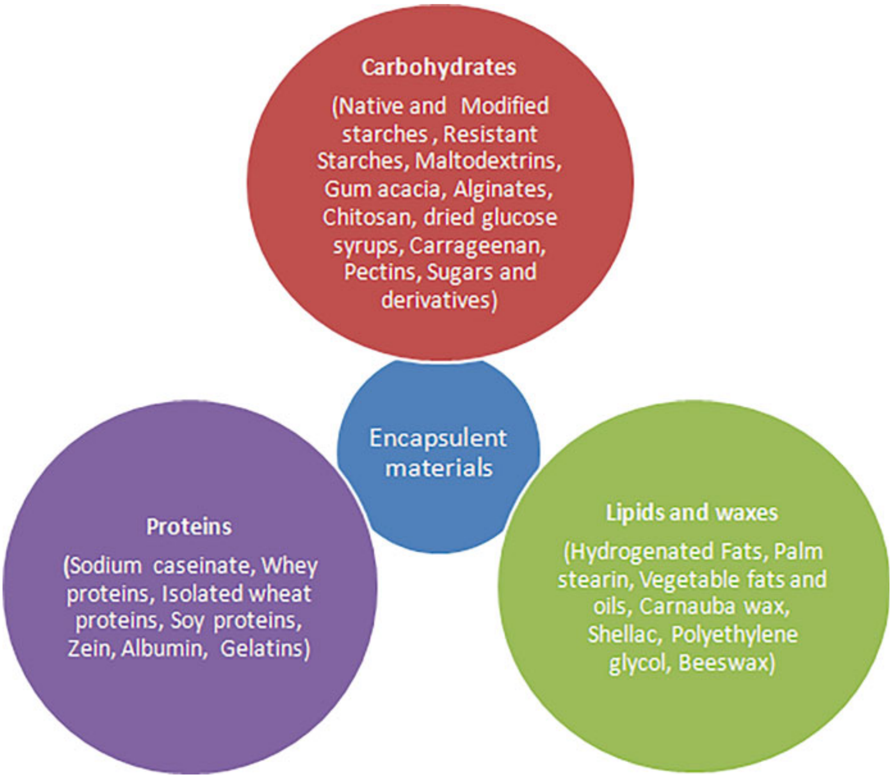

Fig. 2 Encapsulant materials

- Odor or taste masking.
- Promote more comfortable handling (to facilitate the processing of toxic materials or liquids).
- Better processability (improving solubility, dispersibility, and flowability).

The release rate and its mechanism from a polymeric matrix system depend strongly on the solubility of the bioactive ingredients to encapsulate. Highly aqueous soluble bioactive components show faster release rates, while poorly water-soluble ingredients (<0.01 mg/ml) often result in incomplete release due to poor solubility and low dissolution rates for the matrix (Varma et al. 2004). Methods used for microencapsulation in the food industry have been taken from technologies initially developed for the pharmaceutical industry.

Mainly, two methods are used, with some of them explained in detail.

Mechanical process: Emulsification, spray-drying, fluidized-bed coating, centrifugal extrusion, spinning disk, pressure extrusion, hot-melt extrusion.

Chemical process: Simple coacervation, complex coacervation, solvent evaporation, liposomes, cyclodextrin complexation, ionotropic gelation.

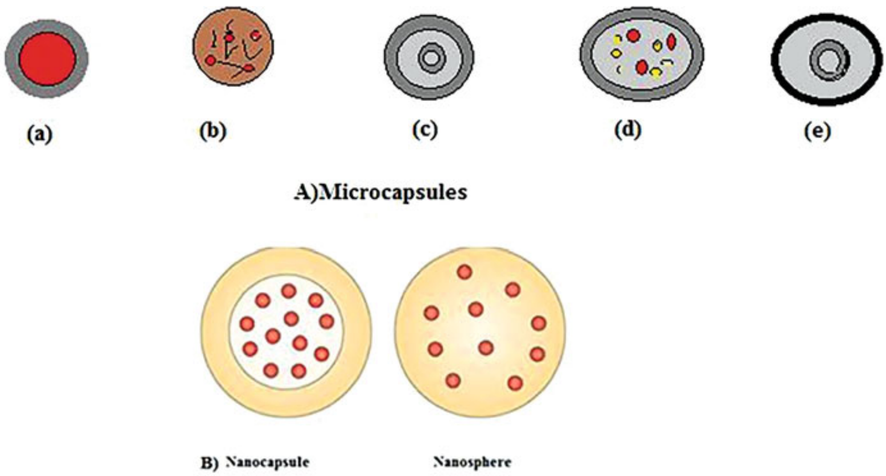

Fig. 3 (**A**) Morphologies of microcapsules: (a) single-core capsule, (b) dispersed core in polymer gel, (c) multilayer capsule, (d) dual-core capsule, and (e) single-core–multishell capsule. (**B**) Nanocapsules and nanospheres

In spray-drying, a homogenous mixture of the active material and wall material in organic/aqueous solution is prepared. This solution is subjected to hot air that dries these microcapsules due to evaporation. In this technique, there is neither solvent residues occurring nor do they need any washing process. It is used in the food industry for microencapsulation of juice pulp and vegetable extract, in probiotics and fish oil (Menezes et al. 2013; Da Silva et al. 2014; Kuhn et al. 2014; Santana et al. 2014; do Amaral et al. 2019).

Extrusion involves incorporating the core in a sodium alginate solution, followed by the mixture undergoing drop-wise extrusion via a reduced caliber pipette/syringe into a hardening solution, such as CaCl2 (Swarbrick 2004).

Coacervation is a method that involves the deposition of the polymer around the core by altering the physicochemical characteristics of the medium, such as the temperature, ionic strength, pH, and polarity (Azeredo 2008). When only a single macromolecule is present, it is known as simple coacervation, whereas when there are two or more than two molecules of opposite charges present, it is called complex coacervation (Freitas et al. 2005).

2.3 *Liposomes*

Liposomes are tiny artificial vesicles of spherical shape which are prepared by cholesterol and natural nontoxic phospholipids. Due to their amphoteric nature, i.e., hydrophilic and hydrophobic, and size, they are impending systems for delivery of bioactive compounds in food (Akbarzadeh et al. 2013). Liposomes are a flexible carrier, can contain both water-insoluble and water-soluble compounds at the same time, and provide target ability (Reza Mozafari et al. 2008). Liposomes have different properties with variability in lipid composition, size, and surface charge and also by the preparation methods (Himanshu et al. 2011). The size of the liposomes can vary from 0.025 μm (very small) to 2.5 μm (large) vesicles having one or bilayer membranes. Preparation of liposomes involves four necessary steps: (a) drying down lipids from an organic solvent; (b) dispersing the fat in aqueous media; (c) purifying the resultant liposome; and (d) analyzing the final product (Riaz 1996; Himanshu et al. 2011). Liposomes have advantages over other methods as they provide selective passive target area, increased efficiency, and stability through encapsulation, control delivery, reduce the toxicity of encapsulated materials, and can be prepared in different sizes (Lasic 1992; Banerjee et al. 2004). They have some disadvantages, such as leakage during long-time storage, difficulty in massive amount of production, variation between batches, etc.

2.4 Nanoencapsulation

Nanotechnology is defined as the understanding and control of matter at dimensions of roughly 1–100 nm, where unique phenomena enable novel applications. British Standards Institution defines nanotechnology as the design, characterization, production, and implementation of materials, structures, devices and systems by controlling the size and shape at the nanoscale (Bawa et al. 2005). The nanoencapsulation system provides many benefits (Shefer and Shefer 2008) as it is easy to handle, is more stable, protects against oxidation, has volatile ingredients retention, is a taste masker, has moisture- and pH-triggered controlled release, has delivery of active ingredients, changes in flavor, has longer organoleptic perception, and has increased bioavailability and efficiency. Nanomaterials for food and bioprocessing applications can be produced from engineered plants or microbes and through the processing of waste materials such as stalks and other cellulosic materials (Robinson and Morrison 2009). Nanotechnology has great potential in improving the efficiency of the delivery of nutraceuticals and bioactive compounds in functional foods to improve human health. It can improve the solubility and bioavailability and also retain the stability of micronutrients and bioactive ingredients during manufacturing, storage, and distribution (Chen et al. 2006). Nanoparticles are colloidal particles with a diameter ranging from 10 to 1000 nm, and they have two forms as nanocapsules and nanospheres (Konan et al. 2002). Nanocapsules are vesicular systems in which the bioactive compound is confined to a cavity bounded by a sole polymer membrane, while nanospheres are matrix scheme where the bioactive mixture is consistently dispersed (Fig. 3B) (Couvreur et al. 1995).

2.5 Nanoemulsion

It is a method that is used to encapsulate substances in small and refers to bioactive filling at the nanoscale range (Lopez-Rubio et al. 2006). The delivery of any bioactive compound to various spots within the body is directly affected by the particle size (Kawashima 2001; Hughes 2005). Nanoencapsulation has the ability to increase bioavailability, improve controlled release, and enable precision targeting of the bioactive compounds to a greater extent than microencapsulation (Mozafari et al. 2006). Nanoemulsions are heterogeneous systems consisting of two immiscible liquids, with one liquid phase being dispersed as nanometric droplets into another continuous liquid phase and stabilized through an appropriate emulsifier.

2.6 Solid Lipid Nanoparticles (SLN)

Particles ranging between 10 and 1000 nm are called nanoparticles, which are synthetically and naturally suitable for delivery of bioactive compounds and reduce toxicity (Mukherjee et al. 2009). The lack of safe polymers with authoritarian and their higher cost restrict the extensive application of nanoparticles to industries (Mukherjee et al. 2009). To overcome the given limitations of polymeric nanoparticles, lipids have been used as an alternative carrier and known as solid lipid nanoparticles (Sathali et al. 2012). SLNs were introduced in 1990 as an alternate carrier system for liposomes, emulsions, polymeric nanoparticles, and other techniques (Pardeike et al. 2009). The size of SLNs ranges from 40 to 1000 nm having a spherical structure (Thatipamula et al. 2011). They are composed of approximately 0.1–30 (% w/w) solid fat in an aqueous phase. Surfactants are also used during manufacturing to enhance the stability of particles, and it ranges from 0.5% to 5%. The SLN can be prepared from one solid lipid or a blend of solid fats (Müller et al. 2002a). The particle size, stability, loading of bioactive ingredients, and its release behaviors depend on the concentration and selection of surfactants and lipids (Blasi et al. 2007). Monoglycerides, diglycerides, and triglycerides, steroids, waxes, and fatty acids are used as lipids during preparation. Depending on the method type of SLNs, they may apply for both hydrophilic and hydrophobic systems (Kim et al. 2005; Das and Chaudhury 2011). Compared with other systems, SLNs are easy in preparation and have high-scale production, low cost, best physical stability, proper release, no biotoxicity of the carrier, and increased drug stability (Mehnert and Mäder 2012; Mäder and Mehnert 2004). They have high physical security and excellent tolerability (Singhal et al. 2011). SLNs have some disadvantages like the growth of lipid particle, gelation, polymorphic transitions, and their less basic incorporation rate due to the crystalline structure of the solid lipid (Mehnert and Mäder 2012; Müller et al. 2002a, b; Yuan et al. 2007). SLN was intended to unite the benefits of liposomes, polymeric particles, and emulsions

(Gramdorf et al. 2008) and to avoid some problems. The bioactive ingredients' mobility can control by controlling the physical state of the lipid matrix of the system (Wang and Wu 2006; Yang et al. 2006). A bioactive substance has much lower diffusion rate; therefore, extended release can be achieved by SLN.

2.7 Nanostructured Lipid Carriers (NLC)

Nanostructured lipid carriers (NLC) a delivery system which is a partial-crystallized lipid particle with average size $\leq$100 nm are dispersed in an aqueous phase containing emulsifier (Tamjidi et al. 2013). NLC is an enhanced, modified system of SLN in which the lipidic phase includes both solid (fat) and liquid (oil) lipids at room temperature (Müller et al. 2002a, b). The NLC or oil-loaded SLNs contain lipid droplets that are partially crystallized and have a less-ordered crystalline structure or an amorphous solid structure, which developed for overcoming the limitations of SLN, and it improves the stability and capacity of loading (Tamjidi et al. 2013). The purpose of NLC formulation is to produce particles in which the oil incorporates into the core of a solid lipid; this leads to a higher loading capacity and controlled release (Varshosaz et al. 2010). The NLC blend with fat has a slow rate of polymorphic transition and low crystallinity index (Jores et al. 2004; Müller et al. 2002a). NLC is mainly appropriate for encapsulating and delivering of lipophilic bioactive molecules and other lipophilic compounds like antimicrobials, flavors, and drugs into aqueous-based foods (Tamjidi et al. 2013).

3 Conclusion

Agro and food industry waste/residues contain high amount of bioactive and antioxidant compounds. So they could be the best sources for these. Utilizing them in food or pharmacy industry could be the best way to reduce losses and environmental pollution and to also ensure the safety of agro and food industry. The potential of various techniques has been well recognized by many researchers as a substitute for conventional packaging and incorporation methods to enhance food protection and control release. However, among the main advantages of using these methods are that several bioactive compounds, such antioxidants, antimicrobials, flavors, and probiotics, can be integrated into the polymer matrix and consumed with the food, enhancing safety or sometimes better nutritional and sensory attributes. Certainly, incorporation of bioactive compounds through all these techniques could be an option to protect them from the atmosphere or the surrounding food, while allowing controlled release. Thus, they can be used to overcome the disadvantages of the straight application of these compounds. However, when bioactive ingredients are added through encapsulation, edible coatings, liposomes, NLCs, and SLNs, mechanical, sensory, and functional properties can be significantly affected. Therefore, studies on this subject are required to apply in food to improve functionality and high sensory performance of the product.

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General Overview on the Water–Energy–Food Nexus

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Abstract In this world, water, energy, and food are extremely important for life, human safety, and sustainable development consideration of our natural resources. Water is used to produce food, where 70% of the available water on earth and 30% of energy are used in agriculture. In addition, the rising population in all over the world (9 billion estimated in 2050) implies the increasing demand for water, energy, and food. From this, it has been noticed that there is a need for a new concept of water, energy, and food in international and national governance. In the last 10 years, this

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concept becomes very interesting to scientists and policymakers. They must work together in order to change our behaviours against water, energy, and food consumption. Therefore, new morphological methods and metrics are elaborated in order to accelerate sustainable development goals. Measurement, assessment, and new approaches were considered in different countries in order to evaluate the water–energy–food (WEF) nexus. Even with this progress in the global world thinking, the risks and threats to WEF nexus still present and affect the effectiveness of this concept.

Keywords Water · Food · Energy · Sustainable development · Circular economy

1 Introduction

Nowadays, humanity starts to face strong environmental challenges due to different human activities. New sources of environmental, eco-friendly, and renewable energy are now on global demand (Li et al. 2018; Haouas et al. 2022; Tallou et al. 2020a, b). The main goal today is to reach circular economy concept, which is one of the objectives of the sustainable development goals (SDGs). This system must protect our environment, insure human life, and strengthen the economic and industrial growth (Winans et al. 2017). Articulating demand for further human resource appropriation, sustaining the resource base, and redistributing power and benefit are the three major groups that exist among the sustainable development goals (SDGs) (Tallou et al. 2021; Si et al. 2019).

The term water–energy–food (WEF) nexus gained importance during the World Economic Forum 2008 and then officially in *Bonn* conference in 2011 'The Water, Energy and Food Security Nexus – Solutions for the Green Economy'. Afterwards, the WEF nexus started to attract European policymaking in their official documents. Nexus new thinking is a global call to all countries in the world to consider sustainable use of the Earth's natural resources. For that reason, the water–energy–food nexus means to consider the pressures and stress created by agriculture, water consumption, and energy production (Hoolohan et al. 2019).

Nexus research activates discussions and debate on how to face positively global environmental change that is now threatening human safety (Zhang et al. 2019). Complexity and uncertainty that characterize the nexus term need more researches and work to gather knowledge and experience from different perspectives and scale. The focal point is to try understanding how metrics in policymaking affect and influence the nexus governance. Considering that metrics can play an important role in stabilizing or challenging how policymakers are representing the world, 'Nexus' thinking needs updated metrics in order to face new challenges (Hoolohan et al. 2019). Three main questions can rise in this consideration:

- What are the new approaches of the nexus concept and how it is related to governance?
- How the WEF nexus can be elaborated on national scale?
- What are the risks and threats to the water, energy, and food nexus?

2 New Morphological Methods to Activate Sustainable Change

Scenario analysis is one of those methods to enhance and accelerate sustainable development. It is already used in different fields of global change and governance, but it is still limited in nexus researches. It also provides many exploring possibilities for future conditions that control and affect the process (Hoolohan et al. 2019). Stepping Up evaluates how to enhance and accelerate the effectiveness of new approaches and innovations that could influence positively the water–energy–food nexus. This method has an objective of understanding the involvement of technological, social, and climatic developments and findings for the nexus innovation concept. The understanding of this concept might accelerate the water–energy–food nexus in order to face the new challenges (Garza 2018).

This method combines the multidimensional changes through the water–energy–food nexus and the different researches in different field studies to produce new scenarios that could help in clarifying the complexity of rapid changes (Zhang et al. 2019). In addition, these scenarios could help to understand how the nexus thinking and decision-making can be enhanced by the water–energy–food research (Garza 2018; Gevelt 2020). In order to reach the effectiveness of decision-making in the water–energy–food nexus concept, it needs deep thinking and the ability to detect the interference between drivers and factors. Therefore, there is a need to build capacities across the different disciplines in order to develop the understanding of the new challenges (Garza 2018; Gevelt 2020).

It is expected in the near future that the integration of water–energy–food (WEF) in the global thinking will enhance the interdisciplinary discussion during the policy development process (Zhang et al. 2018). Comprehensive assessment could help to better understand and provide data about the water–energy–food nexus (Lin et al. 2019). The most important and effective method to evaluate the inter-linkages between water, energy, and food is the life cycle assessment (LCA) method. It can imply the consumption or needs of the natural resources and can estimate the potential changes of WEF in the present and future (Ghodsvali et al. 2019). The second important tool to evaluate and illustrate the practicality of the WEF concept is the GIS-based Regional Environmental Assessment Tool *(GREAT-FEW)*. It was developed by combining a solid model conception, calculation methods, and database. The usefulness of this tool was elaborated in Taiwanese study, where the result showed that the Scenario 1 refers to non-nuclear homeland policy that caused the lowest environmental damage when compared to Scenario 0, which is the baseline, and Scenario 2, which is non-nuclear homeland policy with National Spatial Plan. This result is a consequence of better water consumption, energy structure, and good management of agricultural fields. Therefore, it is obvious that when selecting indicators, the results were affected. We should mention that additional designed indicators are required for each case study (Lin et al. 2019). *GREAT-FEW* allows the users to work on different scenarios for agricultural land use, food needs, energy production, and for sure water demand and consumption. This tool cannot only be used to quantify the environmental influence using the LCA method but also spatial–temporal illustration via a GIS tool interface. The tool will provide policymakers and scientists with both positive and negative results in order to develop new investments and to create new policies for the future (Lin et al. 2019).

Nowadays, there is an important attention to the challenges in developed and developing countries and their transition from unsustainable to sustainable practices. The connection between these three crucial resources offers a conceptual tool for achieving sustainable development. It has become strongly important to understand the interdependencies and interrelationships between the WEF nexus. Looking for new strategies to manage the nexus could contribute significantly to achieving the Global Sustainable Development Goals (SDGs). The WEF nexus, when applied as an analytical tool, becomes important in evaluating progress towards Sustainable Development Goals (SDGs), especially Goal 2 (zero hunger), Goal 3 (good health and wellbeing), Goal 6 (clean water and sanitation), and Goal 7 (affordable and clean energy) (Nhamo et al. 2020) (Fig. 1).

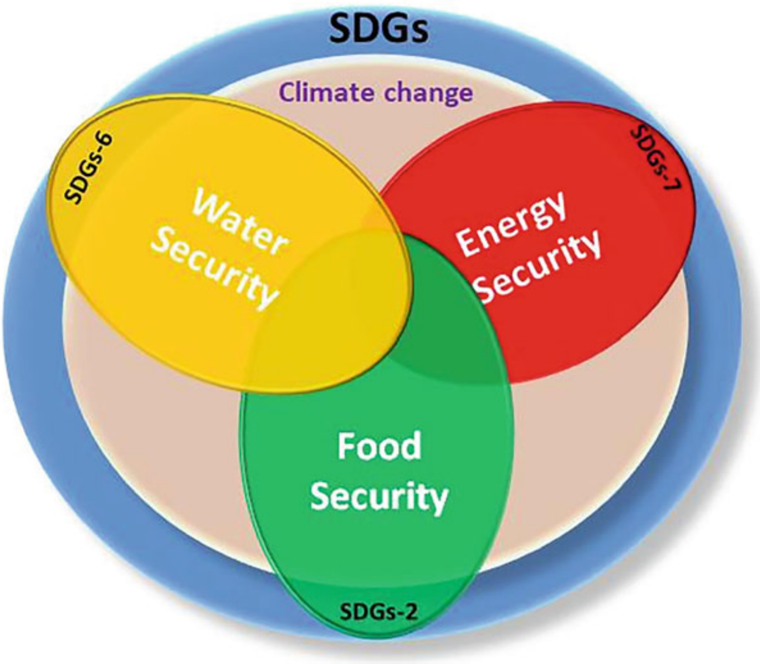

Fig. 1 WEF nexus security and the Sustainable Development Goals

3 The Importance of Metrics in the Water–Energy–Food Nexus Thinking Within the European Commission

The discussion in the European Commission tries to explore the relationship between governance, metrics, and the nexus of WEF *(*Märker et al. 2018*)*. In order to change policy decisions, the metrics must be updated regarding the new interdisciplinary thinking (Gevelt, 2020). It has been indicated that the processes of production and the elaboration of new metrics depend on the institutional practices and will influence the policymakers (Voelker et al. 2019). In doing so, a critical analysis must be done in order to evaluate the role of metrics in environmental governance. It has been highlighted that focusing on the institutional parameters in the way they are elaborated and used, the question of relationship between metrics and WEF nexus, needs more exploration regarding the policy makers' objectives in Europe (Lima et al. 2018, 2019). In the literature, it had been declared that we need to link the multidimensional (institutional, political, and cultural) policymaking to the WEF nexus needs. In this understanding, the biggest challenge is to understand the complexity and the interference between sustainability and the actual modes of consumption and production (Hoolohan et al. 2019; Li et al. 2018).

The majority of studies worked on epistemological problems or conceptual challenges, but only few ones presented the institutional metrics and mechanisms that could limit the consideration of the new nexus thinking and governance (Voelker et al. 2019). Therefore, the nexus complexity could be visible and clear if we use institutional vision that makes environmental challenges relevant. Metrics could build new governance legality and effectiveness. The water–energy–food nexus needs to be considered as a problem of legitimate policy objective if we want to be more precise and broadly within the institutional culture of the European Commission and policymaking. Therefore, it is important to know that the WEF nexus is not only a technical tool, but it is new thinking controlled by exact metrics (Voelker et al. 2019).

4 Measuring the Water–Energy–Food Nexus for Specific Country or Region

Usually, water–energy–food performance of a specific country can be evaluated separately. There are a number of indicators and metrics for each country controlled by the World Bank and United Nations. However, the indicators cannot provide an exact view of any sector because of the presence of different parameters and drivers that interact and affect the general understanding of the nexus. The evaluation of the three sectors of WEF is done according to the available data that are important to understand the ongoing sustainable development of a specific country (Mabrey and Vittorio 2018). Recently, a new approach proposed by the two authors *Simpson* and *Berchner* in 2017 uses an index that involves sustainability level of each country regarding WEF and population (Garza 2018). Three main indicators have been proposed per each sector, which are access, availability, and stability. Those indicators help to obtain a clear understanding and vision about the WEF nexus, and it is possible to notice the status of each sector regarding the available resources. In addition, the sustainable development progress in a specific country or region can be evaluated and measured using these indicators (Garza 2018).

Spatiotemporal disaggregated simulation model was elaborated in *Gavkhuni Basin (central Iran)* using water–energy–food (WEF) nexus concept in order to evaluate water and food supply security considering sustainable environment. This model was used for the first time in *Iran*, where the main contents of it are water, agriculture, population, and energy metrics. This model was developed using the System Dynamics (SD) tool and was used to evaluate the effectiveness of each sector, industrial, domestic, and agricultural water, energy consumption, and environmental safety in enhancing ecosystem-provisioning services in the near future. Results indicated that the combined policies available in the agriculture and environment sectors were the most influencing in changing the WEF system and meeting the *Gavkhuni* environmental requirements (Ravar et al. 2020). The combination policies and instructions (controlling groundwater withdrawal, changing crop pattern, implementation of technology, etc.) increase surface water availability and groundwater security by 5%. In addition, it reduced water used for food production by 18% and energy for water demand by 26%. Policies of the energy sector did not increase the ecosystem-provisioning services. These results have summarized that the food sector was the most influencing and important for the security of water supply and status of the energy system in the *Gavkhuni Basin*. The results also showed the high performance of the WEF (Water, Energy and Food) model in terms of policy impacts of water, energy, and food sectors (Ravar et al. 2020).

Another case study was treated in *Pakistan* using a Life Cycle Approach (LCA) production of molasses-based bioethanol and was interesting in terms of producing food and energy materials related to water–energy–food consumption (Mannan et al. 2018). The water–energy–food nexus for bioethanol in *Pakistan* was described. This Life Cycle Approach (LCA) was used in order to evaluate the four footprint groups (carbon, ecology, water scarcity, and energy production) at the same time with an energetic analysis of bioethanol (Silalertruksa and Gheewala 2019). When comparing bioethanol to gasoline, bioethanol could have better performance regarding greenhouse gas emissions, high-level energetic performance, and safe use in agricultural lands. In contrast, water scarcity will increase because of its high impacts and expenses. Therefore, effective management is required for the best use of this natural resource, which can be insured by new WEF nexus metrics to avoid the risks (Silalertruksa and Gheewala 2019).

In the twenty-first century, deterioration of water runoff in the *Yellow River* region decreased, which results in a clear bad utilization of the available water. The authors of this study identified the most important component from water–energy–food nexus vision. They also established a WEF nexus model for *Upper Yellow River Basin* (UYRB) using the water supplies to the lower and the middle regions that feed the Yellow River, energy production, and food growth in this region (Si et al. 2019). The Multi-start Solver of *LINGO* and the ε constraint method were elaborated in order to reveal the complexity in the WEF nexus concept. This method was used in order to guarantee the general benefits in *Long yang xia* Reservoir that should maintain a high water level in the Yellow River region (Si et al. 2019).

5 Risks and Threats to the Water, Energy, and Food (WEF) Nexus

The complexity of understanding the water–energy–food nexus rises from the diversity and the interaction between many parameters and drivers. The capacity for governing nexus challenges on regional or national scales could be limited by global interdependencies. In their analysis of global production networks, Franz et al. (2018) analysed the global production networks and highlighted the important role of socioenvironmental risks if regions are globally integrated. A fair and equitable consideration of the risks and benefits between sectors and across regions is one of the governance challenges (Raza et al. 2019). Numerous risks threat water–energy–food nexus because of complexity of this concept and due to global environmental change processes, as well as rapid urbanization, climate change, and pollution. Romero-Lankao et al. (2018) worked on the urban side and showed that these kinds of interdependencies increased the risks and threats in the water–energy–food nexus (Sukhwani et al. 2019). It has been illustrated that a precise and clear understanding of these interdependencies is the major key to avoiding the risks and threats between WEF nexus sectors (Arthur et al. 2019). The authors of this work examined how WEF nexus infrastructural systems serve and boost the risks of climate change to urban water–energy–food security system (Namany et al. 2019). The most dangerous risk that threatens the water–energy–food nexus is the wrong understanding and the blur vision of the interferences between the nexus components, and can unfortunately lead to extreme natural damage in those sectors and consequently the human safety (Pahl-wostl et al. 2018).

6 New Strategies to Reduce Water and Energy Consumption in Food Production

In order to reduce water consumption in agriculture and to increase water efficiency, new technical and non-technical strategies and methods were elaborated. These options are soil mulching, deficit irrigation, and drip irrigation. In northwest *China*, the effect of mulching was evaluated regarding soil water storage improvement and soil properties and fertility in maize rotation system. Mulches showed positive effect, and water storage was improved and resulted in warmer soils. In contrast, organic C and total N content of these soils decreased in long term. Therefore, this technique reveals some disadvantages and cannot be considered sustainable (Scardigno 2019). The combination of different techniques and options can be elaborated and can reach the system balance. In northern Greece, different irrigation techniques and technologies were evaluated on cotton. Compared to the sprinkler method, drip technology showed a reduction in water footprint by 5%, and the deficit irrigation there needs about 12% lesser than full irrigation system. In Lebanon, some authors evaluated the effects of mixing mulching with drip irrigation and organic material. Results indicated positive impact of this combination when the water footprint was reduced by 5%. The same results were confirmed also by an Indian study where water productivity was improved after combining drip irrigation and mulching (Scardigno 2019).

Nowadays, irrigation management in agriculture must consider the tempo-spatial variability of plants growth and soil, without affecting the environment, water availability, and food production. Different strategies and solutions were identified in energy optimization in agriculture for water and food production. Some authors proposed new performed tools for energy measurement and control (Scardigno 2019). These techniques identified the weak points in water distribution network and presented the actions that improve the irrigation system. This technique called revised Supply Energy Efficiency uses indicators and data from different distribution network points and the designs using more than one water-feeding source. This method facilitates the decision and data collection in order to improve irrigation efficiency and to reduce water consumption by detecting leak points (García et al. 2017).

Another new method for energy optimization was developed by combining optimization of a pumping station for irrigation and network management using a semi-arranged demand model (Voelker et al. 2019; Winans et al. 2017). This model was elaborated in southern Spain where water scarcity is facing this region. The results showed energy-saving between 5.6% and 25.8% with critical hydrants between 14.5% and 7.8%, respectively (Arthur et al. 2019; Zhang et al. 2018). These strategies must take into consideration the crop requirements and then should not affect the optimal energy and water consumption. Lima et al. proposed a new model called centralized management of collective irrigable areas on demand that reduces and minimizes the energy consumption at farm level. Fixed and variable pressure heads are the two techniques used in this research paper. It has been highlighted that the energy consumed for water distribution can be reduced by 30%. Farmers, in order to control and manage the energy and water consumption in agriculture, should adopt these techniques (Arthur et al. 2019; Zhang et al. 2018).

7 Conclusion

The water–energy–food nexus attracted many scientists and policymakers in recent years. The main objective of working on this nexus concept is to improve the efficiency of natural resource management and to reach the circular economy concept that produces goods, protects the environment, and enhances the human life quality. At the same time, this system must avoid the risks threatening the nexus sectors. In order to reach this global system, new thinking, approaches, and strategies must be established and considered from both the institutional and policy systems. Sustainable Development Goals and circular economy concept are the frameworks of the water–energy–food nexus, but this concept cannot be fruitful without implementation of new metrics and parameters that guide to a better understanding of the complexity of the WEF nexus. Population growth, water scarcity, and limited natural resources increased the pressure on water, energy, and food resources. Therefore, smart management that provides societal goods, protects the environment, and enhances the economy is now an obligation for sustainable development. The complexity and multiplicity of the drivers and interactions between the water–energy–food nexus require mobilization of governance, thinking renovation, and building new capacities to be able to understand the WEF nexus vision and to act exactly in a sustainable way.

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Fate and Impact of Pesticides: Environmental and Human Health Issues

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Abstract The widespread use of pesticides and agrochemicals in general to control pests and weeds has grown during the last century. Because of the exponentially increasing human population, the need to duplicate the yields of crops in order to ensure adequate food availability maintains pressure on the use of these protection chemicals. However, the environment is badly affected by their application which could become a threat to ecosystems biodiversity. Furthermore, several characteristics such as local weather conditions, soils and groundwater quality, application devices, and atmospheric process may affect the fate of a pesticide, its persistence, and mobility by reaching regions far away from the application areas. The present chapter aims to discuss the use of pesticides and their beneficial and harmful effects, pointing out the potential risk of human exposure. The main issues related to pesticide residues and their environmental fate are also described.

Keywords Pesticides · Agrochemicals · Harmful effects · Human exposure · Environmental fate

1 Introduction

Pesticides are widely used during the past three decades, principally in the agricultural sector, to protect crops from weeds and pests and to prevent vector-borne diseases. However, concerns regarding their use have been seriously raised. Indeed, the

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excessive use of these chemicals might impose a serious source of ecosystem contamination by pesticide residues which remained in soils, carried by surface runoff to the terrestrial and aquatic environments where they are bioaccumulated in food chains, resulting in a serious threat to species including humans (Carvalho 2017). It is estimated that only 0.1% of pesticides applied for pest control reach their target, thus the rest spread move throughout the environment (Parrino et al. 2020). Furthermore, pesticides are frequently used in homes as powders and sprays for harmful bugs control. An average of about 150,000 people die each year from pesticide poisoning (Eddleston 2020); according to this, human body exposure to these chemicals has increased considerably being highly vulnerable to their deleterious effects, in particular infants, children, and agricultural farm workers (Mahmood et al. 2016). Moreover, the increasing genetic resistance of many pest species to chemical results in the threatening of pesticides effectiveness, returning eventually to less crop protection, which is a crucial component of food security (Hawkins et al. 2019).

Pesticides are generally used as part of formulation products; for example, Glyphosate, a nonselective herbicide, is formulated with various adjuvants (Van Bruggen et al. 2018) such as polyoxyethylene amine (POEA). Glyphosate formulations with this surfactant are more toxic than those without. Notwithstanding, the use of these substances is extremely needed to increase the crop yields in order to ensure adequate food availability, by preventing hunger which is linked to farm size; 80% of the hungry live in developing countries, with 50% being smallholders (Sati 2015).

This chapter reviews the main issues related to pesticide use their residues, their merits on crops, and above all, the harmful effects of pesticide contaminations on human health, and discusses their environmental fate related to their application.

2 Production and Use of Pesticides: Pollution History

Since the middle of the nineteenth century, the broad-spectrum activity of some pesticides was realized causing a widespread release of these xenobiotics into the environment. One of the first chemical pesticides produced in the United States was Paris green, marking the beginning of chemical insecticide use in 1867 (Cook and Lewis 2015). In the late 1800s, US farmers were using certain chemicals such as calcium arsenate, nicotine sulfate, and sulfur to control insect pests in field crops. Several effective pesticides were synthesized and produced in the period around and after World War II (Mahmood et al. 2016). In the same period, Dichlorodiphenyltrichloroethane (DDT) was introduced as an inexpensive and effective pesticide against insect pests of crops production (Ünlü and Alpar 2018), and was also extensively used to control human parasites and cattle ticks in Europe, North America, and elsewhere (Fig. 1). In 1961–1971, Mansanto developed an herbicide entitled Agent Orange that was used during the Vietnam War (Zierler 2019). As a first published book in 1962, Rachel Carson's groundbreaking work *Silent Spring* pointed out the risks of pesticides, which shook public confidence in their usage. Carson presented the impact of DDT in the food chain causing sudden death of nontarget species in the field (Barratt et al. 2018). Since the 1970s, DDT was

Fig. 1 Application of DDT on humans and cattle around the 1940s. (Photos from the internet)

completely banned in the United States by the Environmental Protection Agency, because of its persistence and broad-spectrum biological activity facing pests, making it toxic to the environment and potentially the human body (Yu et al. 2019). In May 2001, the United Nations has created the Stockholm Convention which targets 12 Persistent Organic Pollutants (POPs) including DDT for virtual elimination (Eugine and Tanyanyiwa 2016; Mahmood et al. 2016). From 2000 to 2015, there were 2303 occupational pesticide poison center exposures; the reported pesticides were insecticides (67.3%), herbicides (17.7%), and repellents (5.8%) (Trueblood and Shipp 2018). Since that time, more than 500 different pesticides formulations are being used in our environment, essentially in agriculture, leading aquatic life and natural flora and fauna into disastrous consequences (Dixit et al. 2019). Nowadays, natural treatments and remedies based on biocontrolling agents including other living organisms are more recommended as a challenge involved with protecting biodiversity and ensuring food security.

3 Organophosphorus and Organochlorine Pesticides

Many of the used pesticides are a mixture of several chemicals which are named active ingredients. Most of these chemicals are designed in a way to disturb the physiological activities of the target organism, leading to dysfunction and reduced vitality (Jayaraj et al. 2016). Two common pesticide classes used in agricultural treatments have organophosphorus and organochlorine chemical structures.

Organophosphorus compounds are named as derivatives of the corresponding parent compounds: acids or hybrids. These chemical compounds are widely used in agriculture due to their low cost and high effectiveness for insect eradications, including parathion, malathion, diazinon, and glyphosate. However, organophosphate pesticide residue is one of the enormous threats to the ecosystem and food security because of their irreversible acute toxicities (Özkara et al. 2016), which is attributed to their ability to irreversibly inhibit the acetylcholinesterase activity that hydrolyzes acetylcholine in the nervous system of a number of species, including humans, which can lead to deadly consequences (Long et al. 2015).

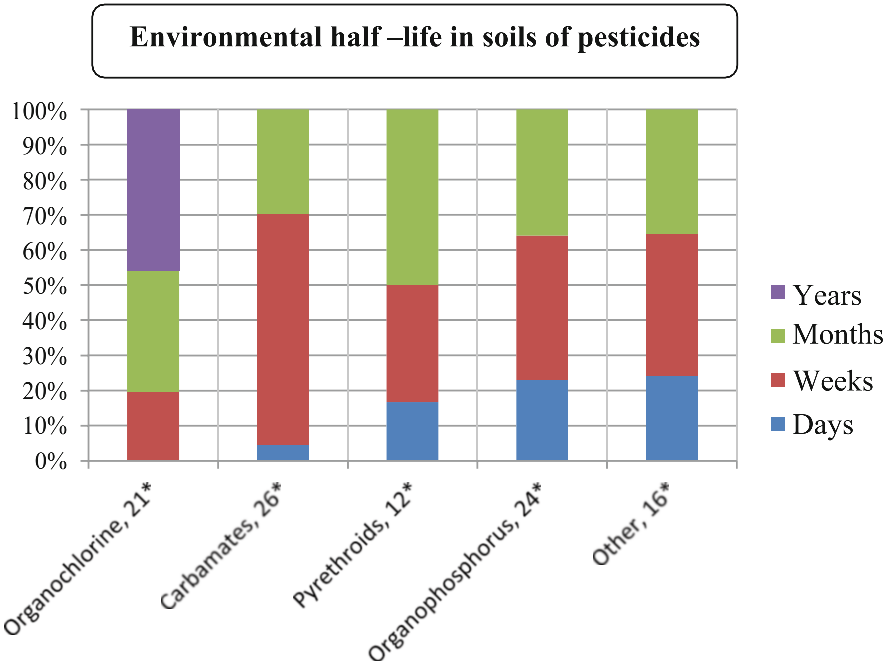

Fig. 2 Environmental half-lives of pesticides in soils by chemical categories. (Carvalho 2017)

Organochlorine pesticides can enter the environment after pesticide applications due to their low polarity, low aqueous solubility, and their high lipid solubility (Chang et al. 2011). The review statistics show that 40% of all pesticides used belong to the organochlorine class (Jayaraj et al. 2016). These compounds such as DDT, hexylcyclohexanes (HCH), toxaphene, heptachlor, and lindane are known for their high toxicity, slow degradation, half volatility, and bioaccumulation characteristics. Moreover, their residues may persist in sediments and soils over days, weeks, and even years (Fig. 2; Carvalho 2017). This situation might pose serious adverse effects on human health and ecosystems.

4 Positive Impacts of Pesticide Use

Pesticide applications bring considerable direct benefits to humans by protecting crops from pests. In the twentieth century, pesticide use increased almost 50-fold to feed the exponential growing human population (Storck et al. 2017) which may even rise in the next 50 years. Indeed, it is estimated that the world population will be of about 9.4 to 10 billion by 2050 according to United Nations statistics (Béné et al. 2015). This would not have been possible without a parallel growth in food production. Furthermore, pesticides are used to directly benefit public health by reducing vector-borne diseases like encephalitis, yellow fever, typhoid fever, typhus, bubonic plague, Zika virus, and malaria, which are transmitted to humans via mosquitoes (Bonner and Alavanja 2017). Insect control is needed to prevent the passage of aflatoxins from insect to plant. This toxin is a carcinogen that can cause a certain type of cancer in humans, alter the natural immune response, and can damage children's development (Vedham et al. 2015). Moreover, economic losses without pesticide use would be much more significant. In a hypothetical case without any pesticide use in the United States, the expected crop yield losses were estimated to be 32% for corn, 57% for rice, and 24% for wheat (Storck et al. 2017). Hence, pesticides play a role indirectly in keeping the food prices under control. Pesticides also protect forests from invasive species of plants and pests and protect buildings and other wooden structures from damage by termites and wood-boring insects. Besides, pesticides play an important role in destruction of diverse organisms which have a negative effect on infrastructure and the materials of everyday life, such as prevention of accelerated corrosion of metal constructions, and maintain the turf on sport pitches and golf courses.

5 Negative Impacts of Pesticide Use

5.1 The Associated Effects on Human Health

The indiscriminate and extensive uses of pesticides are largely known to exert adverse health effects. These effects associated with certain pesticides depend on the type of pesticide (some pesticides are more harmful than others), the concentration and toxicity, exposure duration, and the "route of entry" into the body (absorption through the skin, ingestion, or inhalation). Basically, several epidemiological studies confirmed that extended exposure to pesticides is harmful to humans and is associated with diverse chronic diseases such as cancers, neurodegenerative disease, disruptions of endocrine system allergies, reproductive disorders, asthma, and chronic obstructive pulmonary disease.

5.1.1 Cancers

It has been confirmed that some pesticides as organochlorine were significantly related to the prevalence of prostate and breast cancer. Tinfo et al. (2011) observed an increase in the production of sex female hormones estradiol and estrone which enhance subsequently the mammary gland tumor development. Controversy, other studies demonstrated that there is no evidence between pesticides and breast cancer; this could be explained by the fact that women are less exposed to pesticide applications (Xu et al. 2010). Additionally, Koutros et al. (2010) demonstrated that exposure to pesticides, particularly some insecticides from the organophosphates class, modified 8q24 chromosome and subsequently increased the incidence of prostate cancer. Pesticides are known to cause disorder in the androgen hormone levels (testosterone) through mimicking hormones, affecting enzyme metabolism and disturbing the brain region responsible for the hormone functioning (Ragin et al. 2013). This variation in the androgen hormones might be an important risk factor for prostate cancer. The use of pesticides has been linked to lung disease especially lung cancer. Recently, Bonner et al. (2016) evaluated in a cohort study the association between 43 pesticides and relative risk of lung cancer. They confirmed that the use of chlorimuron, pendimethalin, dieldrin, and parathion leads to the incidence of lung cancer. The prevalence of many types of tumors among a group of German male agricultural workers was studied in a retrospective cohort study (Barthel 1981). Among 169 malignant tumors, 59 cases of bronchial carcinoma were detected in men manipulating continuously pesticides for at least 5 years. The morbidity owing to lung cancer in these cases was significantly higher than that of the male German population. In fact, the increase in morbidity of lung cancer among these German agricultural workers exposed to pesticide might be the result of the effect of various components of pesticides (arsenic, asbestos, chlorinated dibenzodioxins, DDT) used by these agricultural workers with their carcinogenic effect being proven in various experimental or epidemiological studies.

5.1.2 Respiratory Disorders

A population-based study evaluating the association between respiratory symptoms and exposure to pesticides among farm workers confirmed that some respiratory symptoms such as odds of phlegm, chest ever wheezy, and flu are significantly linked with the use of pesticides for smoking and nonsmoking workers (Sprince et al. 2000). In addition, some studies suggested that an increased prevalence of respiratory disorders has been found in specific work tasks, such as spraying and mixing of pesticides (Quansah et al. 2016). Actually, an overview of articles published from 1991 to 2018 revealed that 29 specific pesticides were found to have an association with respiratory diseases and 49 specific pesticides with respiratory symptoms (Sapbamrer and Seesen 2020).

5.1.3 Reproductive Disorders

It is worth to note that exposure to pesticides also affects male and women fertility. Numerous published studies demonstrated the links between exposure to pesticides and female and male fertility disorder (reduced sperm quality, etc.). A study of men consulting for infertility showed that those with less than 50% of mobile sperm had an average plasma concentration of dichlorodiphenyldichloroethane (DDE) higher than patients with normal spermatic mobility (Hauser et al. 2002). Another study carried out on men consulting for infertility showed that circulating concentrations of DDE were significantly associated with an increased risk of having seminal characteristics below World Health Organization (WHO) standards (in particular concerning the concentration, mobility, and morphology of sperm) (Messaros et al. 2009). In Colombia, another study has reported a significant decrease in fertility of women working in the floriculture sector (Idrovo et al. 2005). In France, a recent study of 394 pregnant women showed that concentrations of DDE in the cord blood of children were significantly associated with an extended period necessary to conceive (Chevrier et al. 2013).

5.2 *Threats to Biodiversity*

The abuse and widespread use of pesticides to improve crop yields badly affected populations living in the treated area and consequently led to dramatic declines of biodiversity in agricultural sites (European Commission, 2018).

5.2.1 Effects on Birds

Insecticides, particularly organochlorine (DDT, aldrin, and dieldrin), had direct effects on birds causing reproductive deficiency and increasing mortality rate, thereby a rapid population decline. Other insecticides could have indirect causes on the decline of bird species by disturbing the organisms that constitute their food (Newton 2013). A study conducted by Mineau et al. (2005) confirmed that insecticides when used in granular form and excessively to control the flea beetle (*Phyllotreta* sp.) play a major role in the decline of the bird population in the Canadian prairie. In fact, the impact intensity of pesticides depends on the season of application and exposure time.

5.2.2 Bats as Bioindicators

As bats are bioindicators and victims of agricultural change, Wickramasinghe et al. (2003) evaluated the activity of bat in organic and intensive agricultural landscapes. The results showed that the number of bats was significantly increased in organic farms than on conventional ones. The weak bat activity on conventional farms could be explained by the fact that this type of farm depends on the extensive use of chemical pesticides. Similar results were obtained by other authors who state declines and threatening of bat and arthropods in general due to their exposure to pesticides in the agricultural landscape (Van der Meij et al. 2015).

5.2.3 Bee Declines

Bees are also affected by pesticides. Numerous studies were conducted to identify the toxic effects of pesticides. Recently, Sgolastra et al. (2017) showed that the oral exposure in the laboratory of three adult bee species with Clothianidin, neonicotinoid insecticides, in combination with an ergosterol biosynthesis-inhibitor fungicide (propiconazole) exhibited significant synergistic mortality in all tested species.

5.2.4 Aquatic Animals

Pesticides had also negative impacts on aquatic organisms. Fishes are the most affected by pesticides that contaminate. Numerous studies highlighted the acute and chronic toxicity of pesticide regarding fish and crustaceans (Misha and Verma 2016; Olsvik et al. 2019) and also against microalgae (Dupraz et al. 2019). The majority of organophosphorus and pyrethroid insecticides are toxic to fishes. Zhang et al. (2010) demonstrated that these insecticides, particularly phoxim, permethrin, dichlorvos, bifenthrin, and etofenprox, exhibited a high toxicity against zebrafish (*Brachydanio rerio*; Hamilton & Buchanan). Very recently, Islam et al. (2019) have reported that organophosphate insecticide sumithion exerts a high toxicity to catfish. In fact, the growth retardation and mortality observed for several organisms lead to ecosystem disorder (Vazquez-Duhalt et al. 2005).

6 Behaviors and Fate of Pesticides

During the treatment of crops, pesticides once applied will be subjected to many environmental processes, adsorption, degradation, and movement, which will contribute to their dissipation. These main mechanisms are presented in Fig. 3. Soil, therefore, occupies a fundamental position in regulating environmental pesticides fate, and it will have a dual role in the storage and purification (Barriuso et al. 1994). In fact, pesticides, in the soil, are affected by a variety of physical, chemical, and biological processes which will condition their degradation, their transfer to other environmental systems (water, plant, and atmosphere), and consequently their

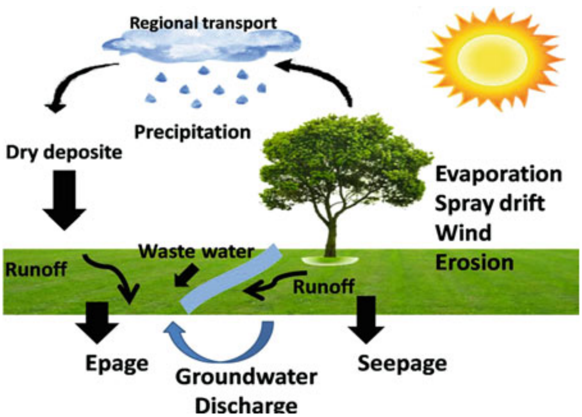

Fig. 3 Behavior and fate of pesticides in the soil (Cook et al. 1995; Harner et al. 1999; Singh et al. 2004; Anju et al. 2010)

potential impact on exposed living beings. In particular, pesticides in liquid and gaseous phases will be more degraded by microorganisms (purification) and also transferred to the groundwater table, while in the solid phase, it remains trapped in soil (storage). The sorption on the constituents of the soil (organic matter and clays) and degradation are the two fundamental phenomena that controlled pesticides' fate in the environment (Arias-Estevez et al. 2008) (Fig. 3). On the one hand, when a pesticide is strongly binding to the soil, its mobility will be low and will be less persistent in the environment (Kerle et al. 1994); thus, the risk of its contamination will also be very weak. On the other hand, complete degradation is when a pesticide is transformed into a mineral molecule, like CO_2, that it is completely eliminated. This phenomenon is called mineralization. Moreover, the rate of pesticides degradation, expressed as the half-life of pesticide molecules in soils, is the length of time required for one-half of the original quantity to break down (Kerle et al. 1994).

Actually, the half-life reflects properly the persistence of a pesticide in the environment, directly related to their degradation. In terms of persistence, pesticides are classified into three categories: nonpersistent pesticides with a typical soil half-life of less than 30 days, moderately persistent pesticides have a typical half-life of 30 to 100 days, and persistent pesticides have a typical half-life more than 100 days (Kerle et al. 1994). Organophosphates, carbamates, phenoxy acid derivatives, chloroacetanilides, pyrethroids, and others are known as nonpersistent (Campos and Freire 2016). Conversely, organochlorine pesticides (OCPs) such as aldrin, dieldrin, endosulfan, dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), hexachlorocyclohexane (HCH), endrin, chlordane heptachlor, and toxaphene are mainly considered as persistent organic pollutants (Bedi et al. 2018). Accordingly, these types of pesticides are very toxic and constitute long-term dangers as they contaminate the food chain and consequently humans and other aquatic and terrestrial systems. In fact, the sorption/degradation couple determines the movement of pesticide from their site of applications. This movement is governed by six processes which are leaching, diffusion, volatilization, erosion and run-off, assimilation by microorganisms, and plants' absorption. The most important possess in the pesticide's movement is leaching, defined as the vertical downward movement of pesticides through the soil profile and the unsaturated zone, which finally reaches ground water, which is susceptible to pollution. Pesticides are normally leached through the soil, precipitation, or irrigation water. Willis et al. (1988) found that 63% of the applied carbaryl was leached by 25 mm/h of precipitation and two hours after the application. Similarly, Pick et al. (1984) found that 2 to 5 mm of precipitation an hour after the application was sufficient to leach 50% of the initial pesticide application. In this same study, it was noted that the resistance to leaching increased when the time between application and precipitation is long. For example, permethrin and sulprofos become more resistant to precipitation leaching when the time between application and initial rain is increased (Willis et al. 1992). Actually, many authors suggest that the contamination of soil, surface, and groundwater could occur due to pesticides leaching. Singh et al. (2007) demonstrated a considerable contamination of soil and surface water of the Unnao region (India) by several persistent organochlorine pesticides namely β- and δ-isomers of HCH and methoxychlor. According to the authors, this contamination is due to the fact that pesticides could leach from soil surface to the lower layers, polluting thereafter groundwater aquifers. Similarly, other authors suggest that the contamination of soil, surface, and groundwater could also occur due to the pesticides leaching from soil to groundwater over time and due to their eventual volatilization and degradation by the soil particles and through surface runoff (Cook et al. 1995; Harner et al. 1999; Singh et al. 2004; Anju et al. 2010).

7 Conclusion

Pesticides are usually considered an inexpensive and a rapid solution for controlling weeds and pests in urban landscapes and have proved an increasing agriculture yield. Irrespective of the extensive benefits which man accrues from pesticides, concerns of their environmental risks and the associated human health effects have been raised by a growing number of scientists and government officials. To help provide food security, we need more epidemiological research contributions to identifying health risks by evaluation of specific pesticides and their mode of action. Indeed, emerging alternative paths in food production, such as including development of genetically modified organisms (GMOs) and their release for international agriculture, must be avoided. Furthermore, the long-term effects of low-level exposure to one pesticide are enormously influenced by concomitant exposure to other pesticides as well as to different pollutants present in water, air, and food. Therefore, exposure pesticides and their undesirable effects on human health can be minimized by using pesticides only when required and in appropriate quantities, and ideally, by the implementation of alternative cropping methods and adoption of good agriculture practices. Moreover, environmental contamination with these toxic chemicals has posed a serious threat on the biological integrity of ecosystems including nontarget organisms and has impinged on over several human generations, which is considered unaffordable. Besides, pesticide residues are found in soil, air, and surface and groundwater across the countries. Using a less toxic formulation or low dose of a toxic formulation can curb the havoc; likewise, awareness for farmers to reduce the uses of toxic pesticides should be arranged. The domain of pesticides still illustrates a certain ambiguity in situations in which people are undergoing lifelong exposure as well as in the dispersion of pesticide residues in the environment resulting in mass killings of nonhuman biota. This ambiguity is further amplified by the imbalance in the number of published scientific papers, reports, newspaper articles, and websites against and for pesticides. Hence, it is the need of time to integrate and to develop health education studies based on aptitude, knowledge, and practices to understand the direct and indirect effects of pesticides on the environment and on human health which must succeed in ensuring safe food production and, thus, security of the food within a viable agriculture production system.

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Metallic Trace Elements in Soil: Persistence, Toxicity, Bioaccumulation, and Biological Remediation

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Abstract Metallic trace elements are toxic substances, nonbiodegradable, highly soluble, easily *bioaccumulate*, and persist for long periods in different spheres of the environment. These properties give them the ability to accumulate in the food chains and induce multiple health damage, even at lower levels of exposures. Consequently,

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there is an urgent need to develop remediation technologies of these elements to protect soil, plants, animals as well as human health. Physical and chemical remediation technologies have the drawback of being often expensive and difficult to implement and release additional waste to the environment.

Phytoremediation and immobilization techniques are frequently listed among the best demonstrated available technologies for remediation of metal-contaminated soils. This chapter comprehensively reviews the different aspects of metallic trace elements as hazardous materials with special focus on their toxicity, persistence, bioaccumulation environmental issues, health risks, and remediation technologies.

Keywords Metallic trace elements · Contaminated soil · Persistence · Bioaccumulation · *Toxicity* · Trophic chain · Environmental issues · Remediation

1 Introduction

Recently, metallic trace elements' contamination issues are becoming increasingly common in the world. Metallic trace elements are natural constituents of the environment, but their excessive use for human purposes like agriculture, industrial, foundries, mining, smelters, coal-burning power plants, and metallurgical has changed their geochemical cycles and biochemical balance. This results in excess release of toxic metals in various ecosystem compartments (Adriano 1986).

In natural conditions, they do not act as toxic elements up to certain concentrations. However, when the concentration reaches the maximum level or up to the final permissible level, they will be converted to toxic elements, and it will lead to harmful effects on the surrounding system (Adriano 2001). These kinds of contaminants are not biodegradable by microorganisms such as bacteria and fungus or chemical degradation and persist for a long time after their introduction. They not only pollute the quality of the atmosphere, water, soil, and food crops, but also threaten the health and well-being of animals and human beings by way of the food chain (Nriagu 1988).

Soil is one of the fundamental components for all living organisms, especially for plants. Soil serves as a medium for growth because it stores nutrients. Abundant amounts of metallic trace elements (MTEs) present in soils cause the reduction in quality and quantity of food-preventing plants growth, uptake of nutrients, and metabolic and physiological processes (Alloway 1995).

Additionally, metal bioavailability greatly determines the behavior and the toxicity of metals in soil and consequently in living organisms. Effects of metals on organisms must be considered within a context of physical and chemical influences affecting transport and fate, as well as vulnerabilities that are unique to individuals, species, populations, and communities.

In order to mitigate the negative effects of MTEs on soil, several remediation techniques such as physical and thermal desorption and chemical methods are recently used (Pilon-Smits 2005; Ali et al. 2013; Mahar et al. 2016). As these remediation techniques have limitation on cost, implementation time, efficiency, and environmental issue, assisted natural remediation (ANR) is then attracting the attention of various researchers due to the advantages of its efficient, cost-effective, and eco-friendly remediation method. It's enhancing natural attenuation mechanisms in soil (sorption, precipitation, and complexation) by adding amendments and/or establishing plants (phytoremediation) to decrease the spread of toxic metals in the environment (Adriano et al. 2004; Perez-de-Mora et al. 2006).

This chapter comprehensively reviews the different aspects of MTEs as hazardous materials with special focus on their environmental toxicity, persistence, bioaccumulation as well as assisted natural remediation techniques and mechanism during their removal.

2 Metallic Trace Elements

2.1 Overview

The concept of "Metallic trace elements" (MTEs) is rarely defined; however, it is gradually replacing that of "heavy metals" (Hooda 2010). This generic term denotes metals and metalloids, which are very toxic and generally present in concentrations less than 1 g kg^{-1} (Adriano 1986). They represent only 0.6% of the total crust, while the 12 major elements (Si, Al, Fe, Ca, Na, Mg, K, Ti, P, Mn, S, and Ba) account for 99.4% (Alloway 1995; Baize 2009). MTEs can be classified into three categories (Adriano 2001) according to their effects and their reactions with the organic and mineral components of the soil:

- The "essential" elements which have a crucial role in the plants' growth and for good reproduction of living organisms.
- The "nonessential" elements which are toxic at certain concentrations and can induce deficiencies in elements' essential, through competition for active sites of important molecules in the physiology of organisms.
- The "indifferent" elements which are neither beneficial nor undesirable.

The majority of metallic trace elements present in the soil belong to the chemical family of metals and metalloids, and they are considered very toxic to humans and the environment. However, only a part of them has significant ecological, biological, and economic interests (Adriano 2001).

2.2 Natural Sources

MTEs are naturally present in soils in small quantities. They are released in different forms during the alteration of the source rock (magmatic, metamorphic, or sedimentary rocks) by the alteration of primary and secondary minerals such as clays, oxides, and carbonates. They constitute the endogenous pool called the pedogeochemical background (Bourrelier and Berthelin 1998).

The term "geochemical background" is often used to designate the concentration of metals resulting from natural, geological, and soil evolution, without any contribution of human activities. It mainly depends on the composition, the location, and the age of the source rock (Baize 2009).

2.3 Anthropogenic Sources

Human activities have not changed the overall quantity of metallic and metalloid elements on the Earth but mainly modified their distribution as well as their chemical form and concentrations. The main sources of contamination are mining activities, the metallurgical and iron and steel industry, industrial activities, agricultural activities, phosphatic fertilizers, pesticides, sewage effluents, biosolids, and urban environments (Rieuwerts et al. 1999; Callender 2003; Douay et al. 2008).

These activities lead to highly polluted soils due to the dissemination of particles contaminated by the wind and/or the runoff of wastes. Generally, this type of soil has a low organic matter content as well as low levels of total nitrogen and phosphorus available (Boularbah et al. 2006; Avila et al. 2012; Baycu et al. 2014). According to metal inputs in soil, we can distinguish two types of contamination:

- *Local contamination* is linked to one or more localized source(s), although those identified are often very close (a few meters to a few kilometers). It's about usually massive inflows, often associated with mining, industrial, and other facilities, both in operation and after closure.
- *Diffuse contamination* mainly results from atmospheric deposits which cannot be linked to one or more identifiable point source(s), as in agriculture (spreading of fertilizers, soil improvers, station sludge purification, phytosanitary treatments, etc.). In this case, the level of contamination may be low, but over large areas.

3 Metallic Trace Elements in Soils

Soils contain different types of compounds that can interact with pollutants. These interactions depend on the physicochemical properties of the soils. MTEs are linked to different constituents of the soil and are present in different chemical forms. They are distributed between the solid phase and the liquid phase of soils. Indeed, their quantity in the soil solution represents only a small percentage of the totality of the pollutant.

MTEs are essentially retained in the solid phase of the soil at the level of which they are distributed in the various organic and mineral fractions (Hooda 2010). They are found in exchangeable form in clays and organic matter (form easily absorbed by plants and having given rise to the term of phytoavailability) (Newman and Jagoe 1994), in the form of complexes or associated with organic molecules (Alloway 1995), included in crystalline phases, adsorbed on particles of oxides or hydroxides of iron, aluminum, and manganese, or even retained in the debris of living organisms which contained them (Kabata-Pendias and Pendias 2001).

The chemical speciation of MTEs is the first criterion which influences their mobility as well as their interactions with soil compounds. The evaluation of the bioavailability and the speciation of MTEs are essential to determine the environmental impact of contaminated soils. They are controlled by the physicochemical parameters of the soil (pH, redox potential, texture, organic matter content, etc.) or biology (plants and microorganisms) (Laperche et al. 2004).

4 Metallic Trace Elements and Soil Pollution

Soil contamination was generally considered less important than air and water pollution. However, in recent years, soil contamination, especially with MTEs, becomes a serious subject of environmental protection worldwide.

MTEs do not explicitly damage the environment in a short period, for their contamination, especially in soil, is difficult to be noticed. Due to their strong latency, MTEs can persist in the environment, and when it exceeds the environmental tolerance or when environmental conditions have changed, they may be activated in soil and cause serious ecological damage.

Recently, soil contamination is amplified by the release of mixtures of metals in the environment, which generates a complex MTEs' contamination. Mixtures of metals may increase the expected adverse effects caused by single metal. In this way, a certain element that might not individually cause environmental effects but in combination with other elements may *become a serious environmental issue* (Calderón et al. 2003). In fact, metals act additively when they are present together, others act independently of each other, and still others are antagonistic or synergistic.

Soil contamination is heavier, irreversible, and hard to remediate. It is difficult to use dilution or self-purification techniques to eliminate metals and to get soils improved. Generally, remediation of soils contaminated by MTEs may require many years (Wood 1974).

The majority of MTEs accumulated in the soil are absorbed by crop plants. These elements are necessary for plant growth in small quantities, and they will be toxic or even lethal in high concentrations (Hänsch and Mendel 2009). The accumulation of MTEs in the soil generates significant yield losses either because the cultivated plants develop less well, or because the soils remain abandoned because they are unsuitable for cultivation (Hossain et al. 2012).

5 Ecotoxicology and Metallic Trace Elements

Ecotoxicology is a discipline that studies the fate and effects of potentially toxic substances in the environment. Among the many polluting substances introduced into ecosystems, trace minerals are particularly damaging because of their toxic and persistent characteristics.

The toxicity of MTEs results in various effects regarding the studied organisms and the quantities present (irritation, sensitization, disturbances in development, growth, respiration, locomotion, reproduction, etc.) up to the death of individuals. It can be evaluated by ecotoxicity tests using some of these effects as a measurement criterion. But in the environment, the toxic effects of metals are not directly correlated with their concentration, because many factors occur, such as the duration of exposure and the climate (Ali et al. 2013).

In addition, the toxicity is different according to the species, some being more sensitive than others, and according to the physiological condition of the organism. Concentration is therefore not enough to predict ecological risks. The investigation should assess the biological availability and speciation of the element.

MTEs can penetrate the body via the skin and through the respiratory and digestive systems. After their penetration, they can interfere in various ways with the body's metabolic function. Some metals are required by the human body, but if they were ingested at higher concentrations, they would have toxic effect. However, other MTEs, such as mercury and lead, have *no health effects*, and they can be detrimental if they are accumulated in the human body (Das et al. 2008).

Persistent exposure to MTEs can generate different functional imbalance in the body, when they are accumulated and used as substitutes for essential elements. For example, lead metal ions can substitute other divalent ions such as Ca^{2+}, Mg^{2+}, and Fe^{2+} as well as monovalent cations such as Na^{+} to ultimately disrupt the biological metabolism of cells (Khan et al. 2010).

Many researches reveal that the accumulation of MTEs disturbs and destroys the main metabolic process of the human body and at the same time leads to an imbalance of antioxidation. Moreover, they affect the function of essential enzymes and the activity of numerous hormones (Gulati et al. 2010).

Researchers also reveal that the MTEs' exposure led to various carcinogenic pathways. Various studies have investigated that carcinogenicity and mutagenicity of MTEs are generally related to their ability to cause oxidative stress. The free radicals that are produced by these reactions cause oxidative damage to proteins and DNA (Wuana and Okieimen 2011; Rodrigues et al. 2012).

6 Factors Affecting the Bioavailability of Metallic Trace Elements

The bioavailability of MTEs depends on several physicochemical (pH, organic matter, limestone, cation exchange capacity, redox potential, etc.) and biological factors (plant species and variety, rhizosphere activities, etc.) (Hinsinger 2001).

PH is a key parameter in controlling the solubility and mobility of metals in the soil. Many researches reveal that increasing pH (alkalinization) of soil is generally associated with reducing MTE transfer to the plants (Adriano 1986; Melgar-Ramırez et al. 2012; Zornoza et al 2013; Midhat et al. 2018).

Soil organic matter plays an important role in the mobility of metal cations through complexation reactions which modify the accumulation and phytotoxicity of MTEs for plants. Indeed, the increase in organic load is accompanied by an increase in the cation exchange capacity (CEC) of the soil and a reduction in the transfer of MTEs to the plant (Hassett and Miller 1977).

The redox potential also plays a role in the behavior of MTEs in the soil. A fall in the redox potential leads to a decrease in the mobility of the metallic element. This reduction in mobility is mainly due to a reduction of sulfates to sulfides with the formation of a precipitate of metallic sulfide (MS).

The mobility and transfer of MTEs are also controlled by carbonates, major components of limestone soils. Indeed, carbonates, by offering a large adsorption surface, are at the origin of the decrease in the bioavailability of MTEs on calcareous soils.

Among the soil components that also provide an adsorption surface for metals are clays, iron, and manganese oxides which also play an important role in controlling the mobility of MTEs (Mench et al. 2003). The time (duration) parameter also affects the chemical speciation of trace elements since the solutions are not necessarily at thermodynamic equilibrium, and the exchange reactions with the ligands can be slow (Wuana and Okieimen 2011).

7 Bioaccumulation of Metallic Trace Elements in Trophic Chain

Food chains are made up of networks formed between primary organisms (drawing their energy from the sun's rays and their mineral environment) and secondary organisms that feed on the former, consumers of these secondary organisms.

The accumulation of MTEs in organisms and the retention of stable metallic elements in ecosystems contribute to the transfer and spread of these elements in the trophic chain and to the expression of their toxic effects. Primary producers (plants for example) can accumulate high concentrations of metals in their biomass via water. They are then consumed by organisms of the second trophic level (animals for example) (Gibbs et al. 2006).

MTEs are bioaccumulated along the food chain, from one level to another, and they are bioavailable. If the metals are biochemically active, they will be absorbed and accumulated at the higher trophic level, but if they are insoluble, they will transit in the digestive tract and will be excreted in the feces. Once absorbed by the body, MTEs continue to accumulate in vital organs like the brain, liver, bones, and kidneys, for years or decades, causing serious health consequences (Zhushan 2019). MTEs can be accumulated in various organs through different mechanisms such as (Ramade 1974):

1. *Bioconcentration* of a substance by an organism is defined as the direct uptake of this substance in the surrounding environment without taking into account its ingestion and assimilation. Bioconcentration is considered a direct way of contamination.
2. *Bioaccumulation* is the process by which toxins enter the food web by building up in individual organisms.
3. *Biomagnification* is the process by which toxins are passed from one trophic level to the next (and thereby increase in concentration) within a food web.

8 Remediation of Metallic Trace Elements

Currently, many efforts are undertaken in several countries to control and manage the releases of pollutants, as well as to speed up the treatment of existing pollution by appropriate techniques, with the aim of preserving humans and ecosystems.

Several techniques can be applied in situ or ex situ to restore soils contaminated with MTEs. *Generally, they are classified into three categories: physical, chemical, and biological techniques* (Simon 1999; Mulligan 2001; Mahar et al. 2016).

The implementing cost of these different techniques is subject to high variability since it strongly depends on site characteristics, nature and concentrations levels of pollutants, and the location of and access to the site (Wuana and Okieimen 2011).

Physical and chemical techniques: They are the most diverse of all other remediation techniques. Physical techniques consist in separating pollutants from the soil or concentrating them in the soil by exploiting the physical properties of the environment and the pollutants. Among these techniques, we can cite for example incineration, excavation, vitrification, confinement, and electrical migration. These techniques do not modify or destroy the pollutants present in the soil (Sheoran et al. 2011; Ali et al. 2013). However, chemical techniques, such as leaching with acids and immobilization using organic or inorganic amendments, use the chemical properties of pollutants in order to make them inert, to destroy them, or to separate them from the contaminated soil. The effect of these treatments reduces the toxicity of contaminants in order to make them less toxic for the environment (Wuana and Okieimen 2011). Usually, a combination of physical and chemical techniques is performed to have better performance of treatment. However, all of these techniques are often difficult to implement, costly, and destructive to the ecosystem (Pilon-Smits 2005; Ali et al. 2013; Mahar et al. 2016).

Biological techniques: They are techniques that use the properties of a living organism in order to decontaminate a target soil. The living organism used can be a micro-organism (bacteria or fungi), a plant (algae, plants, or trees), or a symbiotic association of a fungus and a root of plants, alga, or even an animal such as earthworms. These organisms act on metals (pollutants) thorough various mechanisms such as absorption, accumulation, digestion, transformation, and evapotranspiration. These mechanisms make the pollutants less toxic, less bio-available, immobilizable, or even extractable. There are different biological techniques for soil remediation, which can be applied alone or in combination with other physicochemical processes. Generally, they are classified into two main categories: bioremediation techniques, which essentially use bacteria, and phytoremediation techniques, which exploit the properties of plants.

Bioremediation techniques are based on the metabolism and activity of microorganisms, mainly bacteria, but also fungi. These organisms can be endogenous or exogenous to the contaminated site, and their depolluting properties allow them to transform, immobilize, or dissolve pollutants (Smith 1990; Garbisu and Alkorta 2003). Bioremediation techniques are generally applied in situ. They can be subdivided into several categories according to the biological principle or depollution method implemented (Garbisu and Alkorta 2003). Bioleaching involves microorganisms which extract pollutants fixed in the soil or in certain ores (e.g., leaching of sulfide ores) (Rohwerder et al. 2003). Finally, in biosorption, microorganisms can play a role in the phenomena of mobility and fixing of metals by adsorption, complexation, or accumulation (Barkay and Schaefer 2001). These techniques are low cost but require relatively long action times. In addition, they can only be effective under specific environmental conditions, allowing growth and microbial activity (Vidali 2001).

Phytoremediation is a generic term which combines several techniques and which exploits the potential of higher plants and their associated microorganisms in order to extract, degrade, or immobilize the contaminants presented in the soil, sediments, sludge, and water (surface and underground) (Ali et al. 2013; Mahar et al. 2016).

New technology, low cost, effective, applicable in situ, *non-destructive and environmentally friendly*. It positively impacts soil structure and functions through improving its fertility with increasing organic matter content (Mulligan 2001; Pilon-Smits 2005; Odjegba and Fasidi 2007; Ahmadpour et al. 2012; Ali et al. 2013; Mahar et al. 2016). Actually, phytoremediation is considered as a novel, friendly, low-cost and effective technology which impact posivitly structure and functions of the soil (Mulligan 2001; Pilon-Smits 2005; Odjegba and Fasidi 2007; Ahmadpour et al. 2012; Ali et al. 2013; Mahar et al. 2016).

The generic term phytoremediation comes from the Greek prefix “phyto” (plant) and from the Latin word remedium (Ghosh and Singh 2005). This term combines two remediation strategies: (i) *phytostabilization* (or phytorestoration), which aims to reduce the mobility of contaminants (especially metals) in soil or sediment; (ii) *phytodecontamination,* which aims to reduce the content of contaminants present in the environment. Phytoremediation includes several techniques: phytoextraction, phytostabilization, phytovolatilization, phytodegradation, and rhizofiltration. Among these, the most used are phytoextraction and phytostabilization (Ghosh and Singh 2005; Pilon-Smits 2005; Ali et al. 2013; Mahar et al. 2016).

Phytoextraction (phytoaccumulation) is an in situ technology and requires plants that accumulate and tolerate high metal concentrations in their aboveground biomass, which can be harvested and disposed of or processed for industry or commerce (phytomining) (Brooks 1998; Chaney et al. 2007; Ali et al. 2013; Mahar et al. 2016). There are two phytoextraction strategies: assisted (induced) phytoextraction and continuous phytoextraction (Salt et al. 1998; Ali et al. 2013; Mahar et al. 2016).

The effectiveness of phytoextraction depends on many factors such as the bioavailability of MTEs in the soil, soil properties, speciation of metals, and the target plant species. It can be evaluated by the crop yield (amount of MTEs extracted in kg per ha per year) and the calculation of translocation factor (FT) and bioconcentration factor (BCF). FT corresponds to the efficiency of the plant in transporting the accumulated element from its roots to its aerial parts (Padmavathiamma and Li 2007). It is calculated by the ratio between the concentration of MTEs in the aerial parts and the concentration in the roots. While FBC indicates the efficiency of the plant to accumulate in its aerial parts, MTEs are present in the soil. It is calculated by the ratio between the concentration of MTEs in the aerial parts and in the soil (Zhuang et al. 2007). It is also possible to calculate it from the bioavailable fraction of MTEs.

Plants characterized by FT and BCF greater than 1, high biomass, and deep root system will, therefore, be the most efficient in phytoextraction (Yoon et al. 2006). Generally, hyperaccumulator plants have a BCF greater than 1, with values sometimes reaching 50 or 100 (Ali et al. 2013).

Phytostabilization or phytoimmobilization is the use of plants to reduce the mobility and bioavailability of metals present in the rhizospheric soil or immobilize them by precipitation, stabilization, and/or absorption (Ali et al. 2013; Mahar et al. 2016). The plants used in phytostabilization are hypertolerant species characterized by an exclusion strategy (Berti and Cunningham 2000). This technique is used when rapid immobilization is needed, especially for the preservation of ground and surface water (Gosh and Singh 2005). This strategy is not a depollution technique in the strict sense but a method of rehabilitation of polluted sites aimed to immobilize pollutants in the soil.

The effectiveness of phytostabilization can be improved by the application of organic or inorganic amendments which increase the immobilization and fertilization of soil, called assisted phytostabilization. Amendments application must take into account the quantity applied, the interactions with other components, and the long-term effectiveness. Phytostabilization is more suitable to rehabilitate huge, contaminated areas with high metal toxicity. However, depending on changes in the physicochemical conditions of the environment, there is a long-term risk of remobilization of pollutants and their spread into the environment.

Chemical Immobilization The chemical immobilization process is based on the fixation of MTEs by the application of one or more amendments (or stabilizers), which bind to MTEs in an irreversible form in order to reduce their mobility. It can be achieved mainly through adsorption, precipitation, and complexation reactions which result in the redistribution of contaminants from solution phase to solid phase, thereby reducing their bioavailability and transport in the environment. Moreover, it is a technique usually used in combination with phytoremediation, especially phytostabilization, to reduce the phytotoxicity of the soil and limit their bioavailability for plants uptake (Bolan et al. 2014).

Immobilization by Organic Amendments The mobility of MTEs can be reduced by their complexation with the organic matter provided by compost, manure, sewage sludge, or industrial by-products (Mench et al. 2003; Brown et al. 2003; Perez-Esteban et al. 2012; Alvarez-Ayuso and Garcıa-Sanchez 2003). Soil organic compounds have a high affinity for metal cations due to the presence of ligands or functional groups which can form chelates with metal ions (Kumpiene et al. 2008; Bolan et al. 2014). Metals' retention is more effective as the organic amendment used is rich in fulvic and humic acids (Perminova et al. 2005). *These amendments enhance the physicochemical and biological conditions of soils*, represent a source of nutrients, and allow a reduction in the bioavailability of metals, which increases the chances of successful revegetation of contaminated sites (Castaldi et al. 2005; Kumpiene et al. 2008; Melgar-Ramirez et al. 2012).

Immobilization by Inorganic Amendments An addition of inorganic amendments, such as phosphate compounds, metal oxides, and liming materials to soils, enhances the retention of metals and prevents the increase of metals availability. *Immobilizing inorganic amendments decrease* the bioavailability and mobility of metals and reduce their transfer to food chain via plant uptake and leaching to groundwater (Bolan et al. 2014). The effect of inorganic amendments in the mobility and bioavailability of metals in soils depends on the specific metal(loid), soil type, and the characteristics of the amendment (EC, CEC, pH, and humidification degree). Among inorganic amendments, liming is primarily aimed at ameliorating soil acidity; it is increasingly being accepted as an important management tool in reducing the toxicity of MTEs in soils. A range of liming materials is available, which vary in their ability to neutralize the acidity (Bolan et al. 2014).

The effectiveness of chemical immobilization can be improved by the combination of organic and inorganic amendments. This association ensures better improvement of environmental conditions and therefore increases the chances of successful remediation. Moreover, immobilization techniques are dependent on the nature of the treated soil and the plant cover present in the site (Simon 2005; Mench et al. 2003). An effective amendment should immobilize contaminants in the soil and prevent their spread to surrounding areas while not limiting their uptake by plants. However, some amendments may also contain MTEs, and their application must be appropriately controlled.

9 Conclusion

Soils are the major accumulation focus for MTEs released into the environment by anthropogenic activities. Most metals do not undergo microbial or chemical degradation, and as a result, their total concentration persists for a long time in soils. MTEs' contamination of soil may threaten both humans and the ecological health. They may bioaccumulate in living organisms and be transferred into the food chain. Therefore, background knowledge of the sources, chemistry, and potential risks of these elements in contaminated soils is necessary for the selection of appropriate remedial techniques. Remediation of soil contaminated by MTEs is necessary in order to reduce their toxic effects, make soils more suitable for agricultural production, enhance quality and security of food, and scale down land tenure problems. Immobilization and phytoremediation are frequently listed among the most suitable techniques for remediation of soils contaminated by MTEs. These techniques are recommended for their relatively low cost and simplicity of field application.

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Wastewater for Agricultural Production, Benefits, Risks, and Limitations

Joan Nyika

Abstract Water scarcity and stress is a prevalent concern of both developing and developed nations. The use of wastewater for agricultural activities is a growing solution to this problem as agricultural irrigation is a great freshwater consumer. The drivers to this practice include the rise in urbanization trends, the high demand for food, depleting water resources, and climate variability and change. Production patterns of wastewater showed that developed nations reclaim it while developing nations use it prior to treatment. Benefits affiliated to wastewater agriculture, such as easing the pressure on freshwater resources, expanded agricultural potential even in marginalized communities, and additional nourishment to soils and crops, are highlighted. Risks such as exposure to endocrine disrupters, trace organics, and heavy metals are discussed. Conclusively, wastewater use in agricultural activities has high potential, which can be optimized by adopting treatment technologies and policies that regulate its use toward environmental sustainability.

Keywords Agriculture · Contamination · Developing Nations · Environment · Pollution · Wastewater · Water scarcity · Water stress

1 Introduction

Globally, water resources are depleting due to competing demands in agriculture, domestic, and energy uses of the resource. Expanded production of goods and services to better socioeconomic welfare has resulted in increased use and pollution of natural resources especially water. Many rivers do not reach oceans and are labeled as closed or almost closed, while more than 1.4 billion people live in already closed river basins whose development options are limited according to the World Health Organization (WHO) and as noted by Cosgrove and Loucks (2015).

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Cosgrove and Loucks (2015) reported that more than 2 billion people suffered due to natural disasters such as droughts and floods. Water shortage tendencies are prevalent in peri-urban and urban areas where resources are constrained due to population pressure (Ungureanu et al. 2020). In recognition of these water problems, there is a need to device alternatives to it sustainably.

The use of wastewater is becoming a common practice and a viable alternative to the water crisis. The practice, though pre-existence, is becoming common in agricultural practices, which are the main economic activities of most water-stressed countries (Kanyoka and Eshtawi 2012). Presently, at least 20 million hectares of land in the world are wastewater irrigated according to Mateo-Sagasta et al. (2013). While the use of wastewater for agriculture is a promising road toward improved food and water security, the practice is largely unregulated. In developing countries without clear guidelines and policies on the use of this resource, the situation is dire. These predispositions result in aggravated health risks and other secondary impacts (Ungureanu et al. 2020). According to Karanja et al. (2010), some of the public health concerns due to wastewater irrigation include physical injuries while sourcing it and irrigating, heavy metal, and organic contamination. Although treatment measures are being adopted in line with the concerns, the risk of toxic contamination by enteric viruses and pathogens makes the use of wastewater to replace conventional irrigation uncertain (Ganoulis 2012).

Although there is consensus that wastewater has great potential to improve food security, its safe use is an important integrated water resource management (IWRM) issue that is less understood. In particular, its regulated use is lacking at all governing levels (Karanja et al. 2010). Safety should take precedence because wastewater causes environmental and ecological impacts once it enters food chains. Technologies to treat the resource cannot be afforded by developing countries whose financial and human capacity is limited. These limitations, in addition to unregulated use, do not prevent wastewater use, but rather encourage unsafe practices. Therefore, the need to understand the complex issues in wastewater use, such as drivers and the extent of its use, the associated benefits, and risks and impacts of use in agricultural production, is the focus of this chapter.

2 Drivers of Wastewater Use in Agricultural Production

The increased use of wastewater for irrigation is attributable to a number of drivers, including increased water stress and scarcity, urbanization and population growth, and the rise in water demand for irrigation purposes (Ungureanu et al. 2020). In densely populated regions of developing and middle-income countries, poverty is the driver of wastewater use. In the regions, large volumes of wastewater are produced and treatment capacity before use is limited (Saldias et al. 2017). The high costs associated with treatment and the unwillingness of producers and reusers to contribute to the recovery of incurred expenses hinder the safe use of the resource.

Saldias et al. (2017) noted that the willingness to pay for pollution resulting from wastewater and its treatment remains elusive worldwide. Ganoulis (2012) and Jaramilo and Restrepo (2017) shared similar sentiments. In developed nations, water scarcity is the driver to using reclaimed rather than untreated wastewater (Nyika 2020a). The countries have effective treatment technologies, which prioritize sanitation, environmental protection, and human health in place, though these are expensive. The drivers to wastewater use in agricultural activities are discussed in detail in the following subsections.

2.1 Rising Water Stress and Scarcity

Freshwater resources contribute to about 2.5% of total global amounts, and only about 1% of this amount is available for consumptive uses (Mateo-Sagasta et al. 2013). The resources are unevenly distributed, and about 33% of the total population globally lives in water-scarce areas, which influence their socioeconomic well-being. In addition to physical water scarcity, these countries suffer from economic water stress due to the lack of infrastructure and economic capacity to distribute and store water for users (Mekonnen and Hoekstra 2016). A projection by the United Nations showed that by 2025, 1.5 billion people will live in countries experiencing water scarcity, and 67% of the population will be water-stressed (Mateo-Sagasta et al. 2013). The situation will be prevalent in developing nations of Africa, where 50% of the continent will experience water stress (Mateo-Sagasta et al. 2013). Mekonnen and Hoekstra (2016) reported a water crisis situation where 4 billion people worldwide are living in moderate to severe water-scarce conditions. These populations are concentrated in India, China, Bangladesh, Nigeria, and Pakistan.

Common drivers to water scarcity include pollution, urbanization, and population rise that put pressure on finite and renewable water resources.

2.2 Population Growth and Urbanization

Although most of the wastewater is generated in urban and peri-urban areas, more than 80% of it is never collected or treated, even though one in two people worldwide resides in urban areas (Mateo-Sagasta et al. 2013). Generation of wastewater grows along with urbanization. More than 50% of the world's population already resides in cities, and this percentage is expected to rise by 10% in 2030 (Iacob 2013). The urbanization trend, prevalent in urban regions of developing countries where 60% of the population dwells in informal settlements, pressures cities to provide dwellers with sanitation and clean water for consumptive uses (Andersson et al. 2016).

Higher generation of wastewater in the cities is by consumption and production activities of urban dwellers. Urban people are distributed densely in informal settlements and consume large sums of water that translate to increased freshwater demand and wastewater generation. African and Asian cities have higher water per capita use rates compared to rural areas, yet they have no infrastructural capacity to treat the resultant wastewater prior to discharge (Mateo-Sagasta et al. 2013). Dysfunctional sanitation systems whose access is limited and inequitably distributed among the population and the low priority associated with sanitation in cities complicate the wastewater generation tendencies (Andersson et al. 2016). Consequently, no treatment occurs, and the result is contamination of conventional irrigation water sources that were fresh and had a worse effect on the pre-existent water scarcity state. About 90% of wastewater ends up in freshwater bodies, compromises their quality, becomes an ecological threat, and worsens food insecurity (Iacob 2013). The remaining alternative is to use polluted water for irrigation since it is not potable. Karanja et al. (2010) cited examples of African cities such as Dar-es Salaam and Dakar of Tanzania and Senegal, respectively, that use wastewater for 90% and 70% of their agricultural activities in respective order.

2.3 The Rising Demand of Water Used Agriculture and Food Production

The provision of food for the rising urban population is one of modern day's challenges. According to Mateo-Sagasta et al. (2013), about 2000 to 5000 liters of water is spent to produce an individual's daily food. Irrigation for food production is the best consumer of water worldwide and accounts for 70% and 86% of global withdrawals and total freshwater consumption, respectively (Lupia 2015). In Asia and Africa, food irrigation consumes 85% to 90% freshwater resources (Mancosu et al. 2015). Faced with population growth and a rising demand for food, cities require more water for irrigation despite its scarcity. According to Mateo-Sagasta et al. (2013), more than 1 billion tons and 200 million tons of cereals and meat, respectively, will be required to feed the growing population adequately by 2050, which will increase the global consumption of water for agriculture by 19% more than the current rate. Similarly, Mancosu et al. (2015) reported 50% and 16% rise in irrigation water demand for developing and developed regions, respectively.

The demand for food is a driver for wastewater use because of the sensitivity to water stress associated with agriculture. Mancosu et al. (2015) noted that 80% of global agricultural lands are rain-fed, while the remaining 18% are irrigated and produce over 50% of the world's total food supply. Therefore, a lack of water supply worsened by quality deterioration will significantly reduce both rain-fed and irrigation agricultural capacities unless wastewater irrigation is adopted.

3 Wastewater Types, Use Patterns, and Production Rates

3.1 Types of Wastewater

Wastewater is any water used and discharged from homes, industries, agricultural activities, and businesses (Asano et al. 2007). From the definition, many types of wastewater can be deduced (domestic, industrial, agricultural, and urban wastewater). It is collected by the municipality in a piped system (sewer system). All the types of wastewater on production are collected, sometimes treated, directly discharged to a water system for use, and/ or indirectly supplied downstream as a part of environmental flow (Mateo-Sagasta and Salian 2012). Figure 1 shows a schematic presentation of wastewater processing from production to use. Direct use refers to the diversion of wastewater for irrigation of cropland, forestry, golf courses, and aquaculture, while indirect use occurs once the discharge is done to water sources and used by downstream users after dilution has occurred.

3.2 Wastewater Use Patterns

The uptake of wastewater use in agriculture is influenced by political, regulatory, socioeconomic, and physical environments, which result in varied situations (Raschid-Sally 2013). The interplay of political, regulatory, socio-economic and physical factors results in common wastewater reuse patterns for developing and

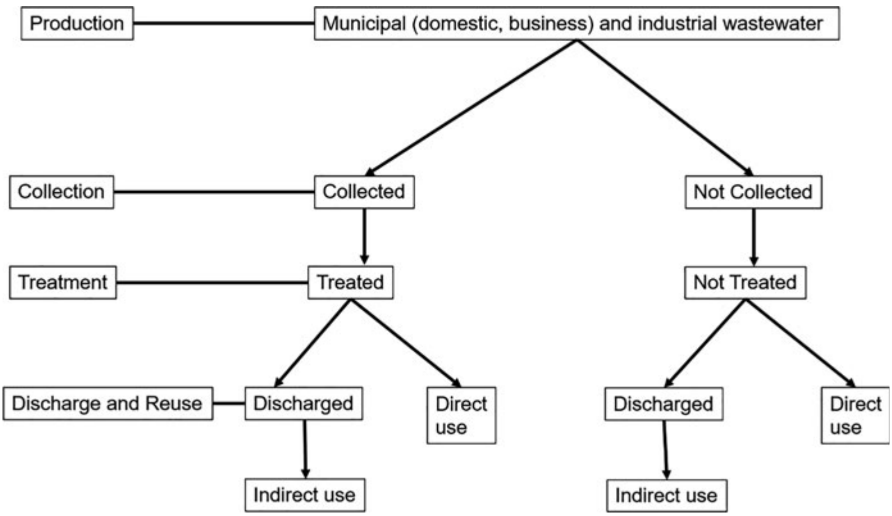

Fig. 1 Schematic presentation of wastewater production and processing before use. (Modified from Mateo-Sagasta and Salian 2012)

developed nations. In developing countries, the resource use is informal while in developed countries, treatment and use are regulated with careful considerations to minimize pollution (Mateo-Sagasta et al. 2013). The magnitude of informal use is higher compared to the formal.

Usage patterns are of five types. First is the direct use of wastewater, which is not treated and occurs among the poor living in water-stressed environments (Raschid-Sally 2013). Although disapproved in many countries due to the associated environmental and health risks, the pattern is the commonest due to the drivers discussed earlier. Case examples include the use of wastewater for agriculture in Pakistan due to the saline nature of the country's groundwater (Ensink et al. 2002) and the use of wastewater from open sewers to irrigate in Karnataka, India, due to high costs associated with alternatives such as groundwater (Bradford et al. 2002). The practice has also been reported in Ghana (Huibers et al. 2004), Kenya (Hide et al. 2001), Nepal (Rutkowski et al. 2007), and Senegal (Faruqui et al. 2004).

The second pattern is the indirect use of wastewater, which is untreated. It occurs when untreated wastewater discharged in freshwater resources, unintentionally or intentionally, flows along with diluted water and is accessed by downstream users (Scott et al. 2004). It is the most expensive pattern of use and occurs in poor developing nations that cannot afford wastewater collection and treatment infrastructure (Keraita et al. 2008). Examples are reported in countries such as Colombia, Brazil, Nepal, India, Argentina (Jimenez 2008), and some parts of sub-Saharan Africa (Keraita et al. 2008).

The third pattern is premeditated use of reclaimed wastewater that occurs in developed nations and is motivated by inadequate freshwater resources and the growing awareness on the importance of conserving ecosystems. Advanced sanitation and treatment methods to reclaim wastewater, which can then be used for landscaping, flushing toilets, and irrigating golf courses and agricultural land, are evident in the pattern (Lahnsteiner et al. 2013).

Fourth, wastewater in the form of untreated sewage can be used for agriculture. This practice occurs in many low-income countries where safety precautions and enforcement legislations on the use of wastewater are downplayed. There is limited data on its use since it is informal (Keraita et al. 2014). The practice is common in South Asia and West Africa, whereby sludge is delivered using septic trucks to farmers (Kvarnstrom et al. 2012). The farmers prefer sludge more than treated wastewater due to its ability to nourish soils and crops from its nutrients (Cofie et al. 2005). Indirect use of sludge is also evident in developing countries without properly designed landfills where solid waste is disposed illegally in water sources and open dumpsites (Mateo-Sagasta et al. 2017).

The use of biosolids formally is the last pattern of wastewater use that occurs in developed countries and is strictly regulated to avoid unwarranted environmental pollution. Biosolids can improve soil fertility reduced by nutrient mining (Keraita et al. 2014).

3.3 Production Rates of Wastewater

Wastewater use practices are never monitored systematically in many countries, and data on production rates is not adequately available (Sato et al. 2013). This is the prevalent trend despite the importance of such data for policymakers and environmentalists in making decision on wastewater treatment and safe return to the environment. The quantity of wastewater that was produced in the domestic and manufacturing sectors in 2010 amounted to 450 km^3, and out of this, only 30% was from the industrial sector (Florke et al. 2013). Data compilation by Sato et al. (2013) reported the global production of wastewater to be 330 km^3 annually, the majority of which was sourced from domestic water uses. AQUASTAT (2014) compiled data on wastewater production in countries whose urban population accounted for at least 80% of the world's population and reported that the annual production was 261 km^3. These values however cannot be relied on since estimates from some countries were outdated. According to AQUASTAT (2014), 40% of generated municipal wastewater is not treated. This figure may not be representative of the actual situation for the following reasons.

1. Wastewater treatment estimates could be lower considering that many treatment plants of developing nations function below their projected capacities (Murray and Drechsel 2011).
2. Data availability on wastewater production and treatment in populous developing countries is unavailable and unreported.
3. Reported data on treatment does not distinguish primary, secondary, and tertiary treated wastewater and is thus not representative of actual situations.

Conclusively, the capacity to correct, treat, and reclaim wastewater is dependent on income where low-income, middle-income, and high-income nations treat about 8%, 28%, and 70% of generated wastewater, respectively (Sato et al. 2013).

Data on the generation of industrial wastewater is sporadic just as that of municipal wastewater production. This trends prevent full exploitation of the resource for reuse and limits the understanding of its production pattern globally. The limitations are worsened by the lack of distinction between the volumes generated and those discharged. According to the United Nations world water development (UNWWD) report (2017), production of industrial wastewater is likely to increase by 100% by 2025 due to the aforementioned drivers to its generation. The manufacturing sector is the greatest producer of wastewater, although total industrial production of wastewater is not a major pollution threat since some industries have adopted treatment measures prior to discharge, though on an *ad hoc* basis.

Data on wastewater use is scanty despite the high potential of the resource to bridge existent water stress situations. Sato et al. (2013) highlighted this observation in a literature assessment on wastewater use publications. In the research, it was noted that out of the publications assayed from 181 countries, only 55 had information on three aspects, wastewater use, treatment, and generation, 69 had information on either two of these aspects, and 57 only had general information. Furthermore, only 37% of the studies had recent and accurate data (Sato et al. 2013). Collating data on untreated wastewater production and use is difficult in developing nations and goes unreported due to its informal use (Mateo-Sagasta et al. 2017).

4 Benefits, Risks, and Limitations of Wastewater Use in Agriculture

4.1 Benefits

Treated wastewater benefits the economy, environment, and human health. The use of this resource is an alternative, which can be adopted in regions experiencing water stress (Jaramillo and Restrepo 2017; Iftikhar-Hussain et al. 2019). The benefit comes in handy as the world is experiencing decline in water resources due to climate change (Becerra-Castro et al. 2015). Another benefit is that wastewater eases pressure on existent freshwater resources. This is because 70% of freshwater uses in the world are consumed for agriculture and use of wastewater will be an alternative irrigation source (Kanyoka and Eshtawi 2012). The practice increases and expands agricultural production to regions experiencing water shortage and promotes food security (Corcoran et al. 2010). Wastewater irrigation will improve water availability as the Food and Agricultural Organization (FAO) proposed (Jaramillo and Restrepo 2017).

The use of wastewater in agriculture avoids costs affiliated with exploiting groundwater at local scopes. In agricultural irrigation, costs affiliated with groundwater drilling and pumping account for 65% of total costs and use of wastewater would reduce these expenses significantly (Lupia 2015). Nutrients found in wastewater serve as fertilizers to nourish soils and plants naturally, which saves on chemical fertilizer costs. According to Corcoran et al. (2010), wastewater will provide an environmental friendly and closed nutrient cycle that minimizes the indirect release of micro- and macro-element to water bodies. Wastewater supplies micronutrients (B, Ca, Fe, Mg, Mn, and Zn) and macronutrients (N, P, and K) (Liu and Haynes 2011) and eutrophication and reclamation expenses of wastewater polluted areas have reduced significantly (Jaramillo and Restrepo 2017). The diversion of this resource for agricultural use preserves the integrity of freshwater resources and promotes the recharge of groundwater of better quality (Toze 2006; Lavrnic et al. 2017). Additionally, wastewater use promoted construction of advanced treatment facilities and serves as an economic instrument to reduce costs of acquiring capital resources and valorizes this resource (Jaramillo and Rostrepo 2017).

4.2 Risks

The use of wastewater in agriculture is associated with some risks, short or long term, that vary in severity to the environment, animal, and humans. Wastewater comprises of pathogens such as bacteria, Schistosoma, viruses, helminthes, and protozoa that intrude from feces, sewage, and infected hosts (Andersson et al. 2016). They come into contact with humans during the process of irrigation and are responsible for water-borne diseases (Ganoulis 2012). The diseases can be of acute or chronic nature and are transmitted by water directly or indirectly.

Wastewater has emerging contaminants (ECs) such as antibiotics, antihypertensive drugs, and analgesics. These molecules are biologically active and persist in the environment leading to their bioaccumulation. Once in food chains from irrigated wastewater, ECs disrupt the endocrine system leading to hormonal imbalances and allergies in animals. Municipal wastewater effluents are primary sources of ECs in addition to agrochemicals (Jackson and Sutton 2008). Use of wastewater for fertigation and as fertilizers is an additional source of ECs. Microorganism resistance is associated with ECs from antibiotics overuse in animals and humans, which are then discharged as urine to water bodies through discharge (Jackson and Sutton 2008).

Wastewater is a source of heavy metals and trace organics. These contaminants are usually ignored, even in countries with defined guidelines on the quality of wastewater used in agriculture despite their high potency (Toze 2006; Lavrnic et al. 2017). The situation is worse in developing nations where wastewater is used without treatment (Saldías et al. 2017).

The presence of high sodium and positively charged ions in wastewater increases the salinity levels of soils. Saline soils interfere with the structure of clay particles and alter its hydraulic conductivity and hence the availability of essential nutrients for plant growth (Toze 2006). Some nutrients such as nitrogen and phosphorous if excessively present in wastewater used in agriculture could poison plants reducing resultant yields.

Wastewater for agriculture is a public concern. Toze (2006) noted that many communities have positive perceptions of ideas to use wastewater, but the same communities are unsupportive to such initiatives and baulk on their introduction closer to their residences. Po et al. (2003) noted that the public have higher concerns about using treated sewage for agricultural purposes compared to stormwater even when the risks associated with the latter are greater. Therefore, intensive scientific communication to reverse the “yuck factor” associated with this practice is needed (Ganoulis 2012; Saldías et al. 2017).

4.3 Limitations

The use of wastewater in agricultural activities has antagonistic environmental effects, especially on the soil matrix. A study by Cossion et al. (2019) on the ecological risks of wastewater irrigation in Bolivia established increased nutrients in soils that had negative effects on the growth of maize and lettuce. Soil microbial community disturbances due to micropollutants accumulation was highlighted as one of the limitations of using reclaimed wastewater in fertigation according to (Chojnacka et al. 2020). Wastewater modifies the physicochemical and microbiological characteristics of soil and influences its structure (Becerra-Castro et al. 2015). The modifications influence soil's production capacity by altering fertility and derailing sustainability of land resources (Toze 2006). Hussain et al. (2019) also reported the accumulation of heavy metals in soils and vegetables irrigated using wastewater. Wastewater irrigation increases the vulnerability to groundwater pollution through enhanced permeability, and leaching ability of soils, the increased bioavailability and bioaccumulation of contaminants (Jaramillo and Restrepo 2017). The effects are a result of increased sodicity, salinity, and nitrogen levels in soils irrigated with wastewater as established in a study by Erel et al. (2019). The potential of eutrophication in aquatic environs following the practice and its resultant pollution is reported as a negative effect (Marinho et al. 2014).

5 Case Studies

Owing to the highlighted benefits of wastewater irrigation, many developed and developing nations are taking up the practice to enhance their water and food security. This section looks at the gains and challenges experienced by a developed (Israel) and developing (Kenya) nation in adopting this practice.

5.1 Wastewater Use for Agriculture in Israel

Israel is one of the driest countries in the Middle East North Africa (MENA) region and suffers chronic freshwater scarcity (Dreizin 2007). Water scarcity in the country is a hydrologic and meteorological natural phenomenon whose effects are exacerbated by climate variability and change (Brenner 2011). Pressured drivers discussed in previous sections, the water state is expected to worsen in the future. Using a number of legal and economic tools, the country has adopted the use of reclaimed wastewater for agriculture. Most notable of these measures is the national wastewater reclamation program that stipulates the measures on using wastewater. Just like other developed nations, the country's national water authority and ministry of environment have teamed up to formulate strict quality standards for wastewater used in agricultural activities (Brenner 2011).

Statistics show that the country treats more than 85% of generating wastewater and uses it for irrigated agriculture (Reznik et al. 2017). This value is considerably high from 75% of used wastewater that was reported by the Israel water authority in 2008 (Bennner 2011). The country has the largest agricultural resilience on reclaimed wastewater in the world where 40% of total agricultural water is sourced from wastewater compared to regions such as California and Spain at 6% and 17% where the practice is also prevalent (Reznik et al. 2017). The country projects to use reclaimed wastewater for more than 50% of its agricultural activities by 2020 (Brenner 2011). Dreizin (2007) noted a 55%, 67%, and 70% growth in the use of reclaimed wastewater, decrease in wastewater discharged in cesspits, and decrease in untreated wastewater discharged to rivers, respectively, as gains to adopting this practice despite the fact that amounts of generation rose by 21%. This notable progress is set to bridge existent water stress gaps especially if wastewater treatment is affected (Reznik et al. 2017).

To manage this practice sustainably, Israel will have to overcome a number of challenges. Apart from the known health and environmental risks of wastewater use highlighted earlier in this chapter, the high use of this resource will result in the modification of the mineral constituents of tap water. This will translate to a need to treat even water previously considered fresh as Brenner (2011) noted. The use of wastewater in agricultural activities will enhance soil salinity, which compromises its productivity in addition to polluting the country's groundwater resources. Brenner (2011) noted that prior to desalination treatment will be necessary to regulate the salt content released to soils. The treatment of wastewater for agricultural use in a closed loop cycle will expose the country to a future environmental crisis as a result of bioaccumulation of persistent emerging contaminants that are endocrine disrupting in animals and humans. This problem according to Brenner (2011) requires that Israel invests more in advanced quaternary treatment techniques for wastewater in addition to bioremediation methods for ECs. The country also requires a strong policy on wastewater valorization and pricing to cater for costs affiliated with its treatment and the opportunity costs of adopting the practice to the environment as Reznik et al. (2017) noted. Although noting the complexity in adopting wastewater use for agriculture from a national scope, Brenner (2011) noted the potential of this resource in enhancing water and food security of Israel.

5.2 *Wastewater Use for Agriculture in Kenya*

Kenya is a water-stressed country located in East Africa. The availability of freshwater was rated at 548 m^3 in 2011, though the figure is expected to reduce to 250 m^3 by 2025 (Ndunda 2013). The drivers for this trend are population increase, high demand for food and agricultural water, climate variability, and a preference for urbanization (Nyika 2020b). In Nairobi, the country's capital city, potable water supplied for domestic purposes is below 100 liters per capita daily and irrigation water is unavailable despite the country having a clear policy on urban and peri-urban agriculture (Ndunda 2013). Consequently, the use of wastewater for urban agriculture is a viable water source. Just like other developing countries, wastewater is used untreated or after partial treatment. According to Karanja et al. (2010), the practice is unplanned and spontaneous and the country lacks a comprehensive policy on the use of wastewater for agriculture. As such, the poor and marginalized are the ones who use the resource for crop production. Although this is the prevailing trend, Karanja et al. (2010) reported that Kenya's urban agriculture relies heavily on wastewater and that most vegetable supplies are grown using this resource.

Despite the high potential of wastewater use for agricultural activities to promote food and water security in Kenya, the practice faces a number of challenges. The first challenge is the lack of a national guideline on the use of wastewater and the quality standards of such water. This has led to the use of 50% of wastewater for agricultural activities before going through any form of treatment (Ndunda 2013). Additionally, many residential and industrial users of water have discharged untreated wastewater to freshwater bodies leading to their pollution downstream (Nyika 2018). According to Cornish and Kielen (2004), the informal and unplanned use and infrastructural distribution of wastewater in Kenya is attributable to the pollution of many city rivers in the country that are used for agriculture in the peri-urban and downstream regions. Pollution of soils with heavy metals and pathogens, the prevalence of water-borne diseases and the risk of soil salinization from wastewater use in some peri-urban areas of Nairobi, Kenya have been documented (Karanja et al. 2010). The need to formalize wastewater use through policies that are cautious of its human and environmental risks in Kenya is, therefore, necessary to optimize its known potential and increase food and water security without promoting further pollution.

6 Conclusions

This chapter explores the potential of wastewater in mitigating challenges of rising food demand amid scarcity of irrigation water and climate variability trends. From the information availed, the following conclusions can be drawn:

1. Wastewater use in agriculture has great potential to ease the current water stress situation in developing and developed nations.
2. Patterns of using the resource depend on the economic potential of countries where developed nations reclaim and treat it while developing countries use untreated wastewater.
3. Wastewater use in agricultural activities has potential benefits and risks. Potential benefits include fertirrigation, expanded agricultural potential to marginalized regions, and eased pressure on existing water resources. Potential risks include exposure to pathogens and ECs to humans, soil salinization, and pollution of water resources.

4. Benefits of using wastewater for food production can be optimized through policy formulation on its treatment and controlled release to the environment.
5. Investment in wastewater treatment and quality reassessment prior to use is indispensable.

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Alternative Crops as a Solution to Food Security Under Climate Changes

Rachid Fghire, Fatima Anaya, Kamal Lamnai, and Mustapha Faghire

Abstract With worldwide growth in population, the food demand has also increased over the years. This demand led to an overexploitation of the water and soil resources. Climate change is one of the most challenging constraints affecting these resources' viability and can influence crop productivity. Hence, our food production system will be in a critical situation. On the other hand, out of thousands of edible plants, the major food sources for the worldwide population are based on three cereals (wheat, maize, and rice). Recently, a number of underutilized crops (such as quinoa, amaranths, millets, Chia, etc.) have attracted important attention due their high nutritional value and ability to thrive in climate changes. Furthermore, these alternative crops present a high capability to grow in marginal conditions such as environmental stress and marginal soil lands and give the opportunity to increase land productivity under the stressful conditions imposed by climate change. Based on these facts, these alternative crops present the future of human nutrition and thereafter the food security of the next generations.

Keywords Alternative crops · Underutilized crops · Climate changes · Pseudo-cereals · Food security · Environmental Impacts · Food Production

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1 Introduction

Climate change impact remains an important challenge for humanity, especially its worldwide impact on agriculture and thereafter on food security particularly under continued population growth. This impact on food security is very heterogeneous between regions and presents a high risk for Africa and South Asia (Knox et al. 2012). Several studies have revealed that around 170 million people are expected to be at risk of hunger by 2080 (Abd-Elmabod et al. 2020). Cox et al. (2018) predict that the crops yield, carbon storage, and water availability are expected to be seriously impacted by the temperature, precipitation, and carbon dioxide. Many researchers show that the projection of agriculture production in the future will decrease due to climate change (Xu et al. 2020; Sarkar et al. 2020; Pareek et al. 2020; Karthikeyan et al. 2020). Therefore, climate change can affect the sustainability of crops by increasing the groundwater resource use in irrigation due to the induced drought periods in the future (Scanlon et al. 2012; Yao et al. 2020). Under this condition, the irrigated cropland surface will decreased and probably transformed to the rain-fed agriculture system, and consequently a real decrease in food production (Elliott et al. 2014). Apart from these factors, other factors can increase global food insecurity such as soil properties' influence, pests, and diseases (Karthikeyan et al. 2020). Considering both direct and indirect effects of climate change on agriculture and given the increasing food demand, the situation imposes an adaptation of farmers to the future climate condition to promise food productivity. Therefore, introduction of new crops with high resistance to biotic/abiotic stress induced by climate change, with a wise management of all kinds of water resources (river, lake, and groundwater) through improving irrigation technic and storage, remains unavoidable to reach sustainable agriculture practices and maintain food security. Recently, alternative crops have received more attention as one of the solutions to sustain farm productivity by diversification of the agriculture systems and provide a new strategy to secure food and nutritional security especially in a vulnerable environment (Ismail et al. 2019). The aim of this chapter is to review the effect of climate change on some factors, with a direct effect on agriculture, and to highlight some of the important alternative crops, which can play a key role in providing an important food resource and thereafter maintain the food security.

2 Climate Change Effects on Soil Quality

The soil quality has been degrading worldwide and presents a global multiface phenomenon (Koch et al. 2013). This decline limits the capacity of soil to provide economic goods and ecosystem service (Lal 2010). Therefore, the ability to assure the world growing population induce widespread pressures on soil; in consequence, soil function impacts seriously biodiversity, freshwater retention, agriculture productivity, and food security (Koch et al. 2013). It has been estimated that within the soil

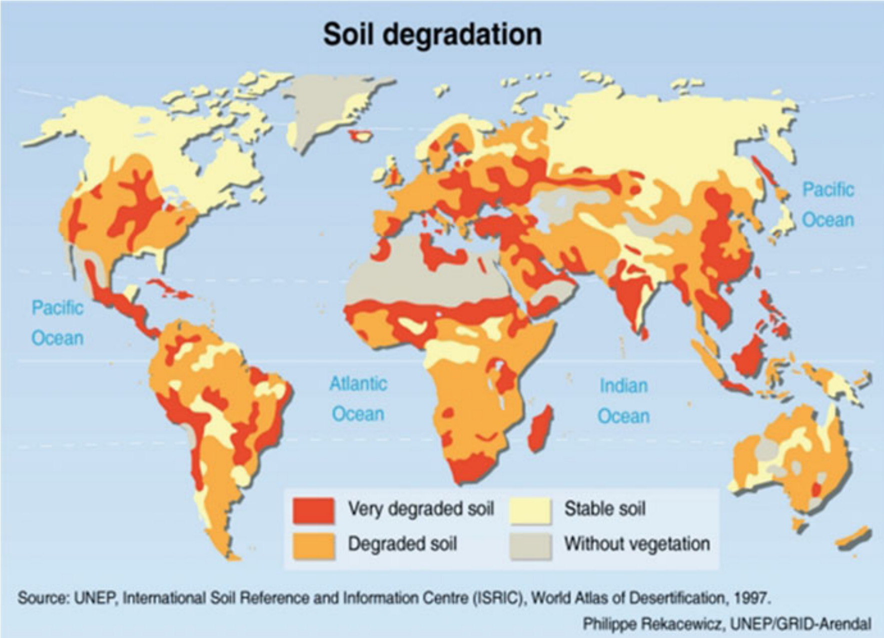

Fig. 1 Estimates of the level of soil degradation at a global level. (Source: Rekacewicz, public domain for nonmarket purposes). https://www.grida.no/resources/6338

exists 98% of terrestrial biodiversity, and this soil provides 97% of our food (Saxena et al. 2018). As the quality of soil is decaying over the world, the United Nations Convention to Combat Desertification (UNCCD) launched an initiative to address the issues that can help tackle biodiversity loss and climate change (McBratney et al. 2017). Gomiero (2016) indicates that some natural processes of soil degradation (salinity compaction, erosion, soil carbon and fertility loss, and acidification) can be accelerated because of inappropriate farming practices or excessive land clearing. The FAO (2011b) highlights that poverty is strongly related to soil degradation; therefore, food security, especially in poor regions, is under a major threat because of soil degradation. This degradation, as estimated by the FAO-UNDP project Land Degradation Assessment in Drylands (Fig. 1), is categorized as follows: 25% of all global land falls in the "high degradation or highly degraded lands" class, 36% is of the "stable land, slightly or moderately degraded" type, and 10% is considered to be "improving land" (FAO 2011b; Bindraban et al. 2012).

3 Climate Change Affects Water Availability

Agriculture consumes majority of available water worldwide, amounting to more than 85% of global use (Dalin et al. 2019; Brauman et al. 2016). This higher water demand in many food regions led to an overexploitation of resources in response to the orientation of the production to the exportation under the globalization of the food system (Dalin et al. 2019). On the other hand, Bruinsma (2003) and Wu and Ma (2015) indicate that just 20% to 25% of harvested crop areas are irrigated, and these areas produce 45% of total food production. However, the prediction of the world growth population impose an increase of the agriculture production by 70%, consequently an increase in the water irrigation demand (Alexandratos and Bruinsma 2012). Sohoulande and Singh (2016) also noted that water quality, quantity, and the hydrogeological cycle will be significantly affected by climate change. Then the availability of water will be affected, and the surface water availability patterns are expected to change in a warming climate (Qin et al. 2020), as the evapotranspiration returns 60% of global average precipitation to the atmosphere, and by the end of the century, it could reach 80% (Pan et al. 2015). Although at the worldwide levels, surface water provides the majority of irrigation water (Siebert et al. 2010), Elliott et al. (2014) predict a conversion of 20 to 60 Mha of irrigated cropland to rain-fed system by the end of the century under the limitation of freshwater. This situation induces more pressure on the nonrenewable water resources in irrigation. The groundwater is the source of approximately 20% of irrigation globally, and this amount has tripled from 1960 to 2000 (Dalin et al. 2019). As a result of climate change, drought will affect many regions and groundwater will be more solicited to provide an alternative source of water, which will lead to fast aquifer depletion (Ward et al. 2019). Further, the reduction and the rationalization of water use, especially in irrigated agriculture, are of importance (Nechifor and Winning 2019; Jägermeyr et al. 2015). Researchers have widely discussed many techniques to improve water use efficiency in agriculture, from the deficit irrigation application to improve water productivity (Fghire et al. 2015b), maximize the useful fraction of water irrigation by drip irrigation (Nouri et al. 2019), replacement of other water sources in water-scarce areas by using rainwater harvesting technique (Durodola et al. 2020), reduce unproductive soil evaporation by soil mulching (Mo et al. 2016), improve the capacity of soil to hold water by tillage conservation (Abbas et al. 2020), and adaptation and introduction of new resistant crops to drought to reduce water shortage vulnerability (Issa Ali et al. 2019; Fghire et al. 2017; Houshmandfar et al. 2019).

4 Food Security and Agriculture Food Production

The agricultural productivity will decrease in the future as a consequence of climate change (Carsan et al. 2014; Muñoz-Rojas et al. 2017; Jat et al. 2018; Lopez-Ridaura et al. 2018). However, if farmers adapt to this climate change situation, this productivity can be increased (Abd-Elmabod et al. 2020; Lopez-Ridaura et al. 2018). In this context, researchers have been proposing many solutions to adapt to new agricultural patterns and mitigate the negative effect of climate change. The intensification of agriculture to produce more has been widely discussed, even though this strategy can aggravate the capacity of the society to preserve their long-term productivity and natural resource (Hazell and Wood 2008; Borelli et al. 2020; Ayantunde et al. 2020). Another concept is that vertical farming (hydroponics, aeroponics, etc.) provides a promising future, especially in urban and peri-urban areas (Thomaier et al. 2015). These techniques could significantly reduce water use and soil-related cultivation problems, and they can provide greater yields compared to traditional farming with a minimum environmental impact (Jones Jr 2016; Al-Kodmany 2020). However, the application of this concept is not easy because of the economic feasibility and the lack of experience (Al-Kodmany 2020).

In situations where no measures are taken and farmers do not adapt to the climate change, we will have to face a decrease in the food production (Abd-Elmabod et al. 2020; Zhao et al. 2017). This decrease in agriculture production is affected by complex interactions between climate conditions, soil characteristic, water availability, and management practices (Elliott et al. 2014; Zhao et al. 2017; Sloat et al. 2020). However, the assessment of the relationship between climate change and crop productivity relies upon a combination of modeling and measurement (Challinor et al. 2009). Several studies have examined the yield variability of major crops such as wheat, maize, rice, and soybean under the impact of climate conditions, drought, precipitation, and soil physiochemical characteristics and have revealed the negative impact of the above factors on these crops (Wang et al. 2020; Li et al. 2020; Abd-Elmabod et al. 2020; Sun et al. 2019; Ayantobo and Wei 2019; Zhang et al. 2018). Food security is a state where both the availability and accessibility of food are ensured, which cannot be achieved unless farmers adapt to alternatives such as water management, crop rotation, and introduction of new alternative crops that can tolerate climatic changes.

5 Alternative Crops

The agriculture sector will face many handicapping constraints in responding to the world's needs in the future with the growing population and the declining productive agriculture land per capita in many countries (Bruinsma 2003). Furthermore, climate change (high temperature, variable precipitation, and soil degradation) threatens agriculture productivity and imposes difficult growth conditions on the production of major crops (Massawe et al. 2016; Abraham et al. 2014; Thornton and Laura 2012). Moreover, the world is based on a few major crops (wheat, rice, and maize), ignoring many crops with high nutritional value to satisfy the growing food demand.

The alternative crops, which are rich in proteins, minerals, and high-content vitamins, offer many nutritional properties and health benefits (Karelakis and Tsantopoulos 2017) and include varieties that have specific characteristics. They provide important perspectives for exploitation, have sufficient adaptation capacity in various climatic conditions, and, at the same time, are characterized by less variability in yields from year to year, mainly due to a wider range of crops used in contrast to conventional agriculture (Chappell and LaValle 2011).

Karelakis and Tsantopoulos (2017) report the major advantages of alternative crops as follows:

- They support the economic viability of especially the smaller-scale farms.
- They are able to meet modern nutritional needs.
- They can maintain or improve the resources on which they depend, focusing on soil protection, nutrients' recycling, and biodiversity protection.
- They can provide an opportunity for farmers to exploit their knowledge and skills.
- They can resist market volatility.
- They can make more efficient use of nonrenewable resources.
- They can incorporate, as appropriate, the natural biological cycles and pest management tools in production practices.

Alternative crops would diversify agriculture systems by providing a new cropping option to the farmers (Rao and Shahid 2014; Van Hoang and Tran 2019) and thereby improving food security. Many of the alternative crops are able to produce a good yield under different abiotic stress (Umesh et al. 2019).

Quinoa (*Chenopodium quinoa*) The *chenopodium* genus includes about 250 spices and is a pseudo-cereal free of gluten originated from the Andean region (Bhargava et al. 2006). It is considered as a climate change-resilient crop due to its potential to adapt and grow under extreme conditions, such as drought, salinity, and frost (Issa Ali et al. 2019; Fghire et al. 2015a, b, 2017; Koyro and Eisa 2007; Jacobsen et al. 2005). Thereafter, quinoa presents a strategic crop to answer the food security problems due to low-cost production, high nutritional value, wide genetic variability, and high agronomic adaptations. Therefore, FAO (2011a) considers quinoa as an alternative food for limited food production countries.

Amaranth (*Amaranthus* spp.) The genus *Amaranthus* includes 50 to 70 species and is a part of the Amaranthaceae family (Costea and DeMason 2001; Das 2016). It is grown in tropical and temperate regions and is originated from Central America, where it was an Aztec and Mayan food (Joshi et al. 2018). The amaranth is an underutilized alternative crop with high nutritional value (Rastogi and Shukla 2013), and all parts of this plant are edible. It is grown as a pseudo-cereal in India and the Americas and as leafy vegetable in Southeast Asia and Africa (Ismail et al. 2019). This plant presents high adaptability to a wide range of soil and climate conditions, especially heat and drought, as it is a C4 crop species (Joshi et al. 2018).

Millets It is a term that designates several kinds of grasses (Poaceae), most of which belong to the subfamily *panicoideae*, with the exception of the finger millet (*Eleusine coracana* L.) and the teff (*Eragrostis tef*) belonging to the chloridoideae subfamily (Madella et al. 2016). Due to its adaptation to hot and dry areas, millet is an important food source in arid areas. Moreover, millet can be stored for long-term periods without losing quality and present a high nutritional value with an interesting property of resistance to pests and diseases. Millets are important crops for food security (Adhikari et al. 2015; Petersen and Augustin 2006; Msangi 2014). Millets can adapt to poor soil and low-moisture lands. The most cultivated varieties of millet are pearl millet and finger millet (Thornton and Laura 2012): The first one is most adapted to semi-arid regions as a dry-land crop, while the second is adapted to subhumid areas in uplands (Saxena et al. 2018).

Chia (*Salvia hispanica*) It belongs to the Lamiaceae family and is originated from Central America. It is characterized by very small seeds, white or blue flowers, leaves with different degrees of pubescence, and a subangular stem. It is a self-pollinating plant (Vastola 2015). Chia seeds are free of gluten and rich in $\omega - 3$ fatty acid proteins and antioxidants (Joseph and Evolution 2004). Chia can be grown under marginal growth conditions such as semi-arid environment; further, Chia can be a good alternative crop to replace existing forage crops (Bochicchio et al. 2015). Therefore, Hussain et al. (2020) indicated that the cultivation areas under Chia are increasing as a result of its ability to produce significant yield even on marginal lands.

The Triticale (*Triticum secale*) is a hybrid cereal obtained from wheat and rye (*Secale cereale*) hybridization. It combines both parents' properties, receiving rye's adaptability to marginal soils, drought tolerance, and resistance to disease and wheat's quality of food products (Hussain et al. 2020). It is mainly used as animal feed, but in recent years, there has been an increasing interest in utilizing triticale for food production because it is rich in mineral nutrient, vitamins, and protein contents.

6 Conclusion

The most important challenge for humanity in this century is climate change, especially its impact on the agricultural production. With the continuing growth in population, people suffering from hunger will also increase in the future. Thereafter, research must be focused on the food security preservation and adaption strategy to cope with climate change severity. Further, the diversification of cropping culture remains one of the important solutions. Crop diversification based on the salt- and drought-tolerant species is the key to improve marginal land use and production. This strategy is likely to be a very cost-effective option with high economical return. The introduction of the alternative crops with high tolerance to marginal conditions can provide an interesting strategy to reach sustainable agriculture with fewer inputs and higher yield.

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Part II
Food Security Policies and Smart Food

Food Security, Legislation, and Regulations: Reading of Law Relating to Food Safety in Morocco

Mohamed Lharoual, Adil Ouatat, Tawfik El Moussaoui, and Hicham Chatoui

Abstract The regulation of food safety in Morocco falls under the law 28/07 on food safety promulgated on February 11, 2010. It is a comprehensive food safety legislation that includes 30 articles.

This law includes several regulations currently in force. It aims to target different goals, scope, and definitions of some concepts. The second title deals with the conditions to put food products and foods for animals in the market. It also refers to competence, research, and finding of offenses and mentions the offenses, their penalties, and some transitional provisions.

Keywords Food safety · Legislation

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1 Purpose and Scope of Law 28-07[1]

– It establishes general principles for the safety of food and feed products. It also determines the conditions under which primary products,[2] food products, and animal feed must be handled, treated, transformed, packaged, conditioned, transported, stored, distributed, displayed for sale, or exported as a safe product, whether fresh or processed, regardless of the processes and systems used for preservation, processing, and manufacturing.
– It provides for general requirements to allow only safe products to be placed on the market, in particular by laying down general rules on hygiene, sanitation, use of cleaning and disinfecting products, permissible contamination thresholds in primary products, food products for human consumption, and animal feed to which they must respond, including those standards that are mandatory.

[1] Bulletin Officiel n° 5822 du 1er rabii II 1431(18 mars 2010), p.214

[2] Voir article 53 du décret n° du décret n° 2-10-473 du 7 chaoual 1432 (6 septembre 2011) pris pour l'application de certaines dispositions de la loi n° 28-07 relative à la sécurité sanitaire des produits alimentaires; Bulletin Officiel n° 5984 du 8 kaada 1432 (6 octobre 2011), p. 2193.

Article 53:

« Les produits primaires et les produits alimentaires sont conformes lorsqu'ils:

1. proviennent d'un établissement ou d'une entreprise autorisée ou agréée conformément au présent décret;
2. ne renferment pas de substances interdites administrées aux animaux d'élevage dont la liste est fixée par arrêté du ministre chargé de l'agriculture;
3. ne renferment pas d'additifs alimentaires autres que ceux figurant sur la liste et dans les limites autorisées;
4. ne contiennent pas de résidus des produits pharmaceutiques, phytosanitaires et de contaminants de la chaîne alimentaire au-delà des limites maxima autorisées;
5. sont conformes aux critères micro biologiques et toxicologiques dans les limites autorisées;
6. sont emballés ou conditionnés dans des emballages ou conditionnements composés de matériaux destinés à entrer en contact avec des produits alimentaires dont la composition et l'emploi sont fixés par arrêté conjoint du ministre chargé de l'agriculture, du ministre chargé de la pêche maritime, du ministre chargé de la santé et du ministre chargé de l'industrie et du commerce;
7. sont étiquetés conformément à la réglementation en vigueur.

Les listes et limites visées aux 3), 4) et 5) du présent article sont arrêtées conjointement par le ministre chargé de l'agriculture, le ministre chargé de la pêche maritime et le ministre chargé de la santé. »

– Voir aussi l'arrêté conjoint du ministre de l'agriculture et de la pêche maritime et du ministre de la santé n° 156-14 du 15 rabii I 1435 (17 janvier 2014) fixant les limites maximales autorisées de résidus des produits phytosanitaires dans ou sur les produits primaires et les produits alimentaires ; Bulletin Officiel n° 6322 bis du 9 rabii I 1436 (1er janvier 2015), p. 238.
– Voir aussi l'arrêté conjoint du ministre de l'agriculture et de la pêche maritime et du ministre de la santé n° 1795-14 du 14 rejeb 1435 (14 mai 2014) fixant la liste et les limites des additifs alimentaires autorisées à être utilisés dans les produits primaires et les produits alimentaires, ainsi qu'aux indications que doivent porter leurs emballages ; Bulletin Officiel n° 6322 bis du 9 rabii I 1436 (1er janvier 2015), p. 425.

– It indicates the mandatory rules for consumer information, in particular by labeling primary products, food products, and animal feed and determining accompanying documents.

In general, the provisions of this law cover all stages of production, handling, treatment, transformation, packaging, conditioning, transportation, storage, distribution, exposure to the sale, and export of primary products, food products for human consumption, and animal feed.

2 The Category Excluded from the Scope of the Law

– Primary products intended for private household use and for the preparation, handling, and domestic storage of food for private domestic consumption.
– Medicines and all other similar products for preventive or therapeutic use in the fields of human or veterinary medicine,[3] as well as cosmetic products
– Tobacco, products derived therefrom, as well as psychotropic substances and other similar substances which are the subject of specific legislation.

In particular, in law 28-07 relating to the health safety of food products, traceability is the ability to trace, through the food chain, the path of a primary product, a food product, an animal feed, or an animal producer of primary products or food products, or a substance intended to be incorporated or likely to be incorporated in a food product or an animal feed.

[3] Voir article 20 du décret n° 2-10-473 du 7 chaoual 1432 (6 septembre 2011) pris pour l'application de certaines dispositions de la loi n° 28-07 relative à la sécurité sanitaire des produits alimentaires; Bulletin Officiel n° 5984 du 8 kaada 1432 (6 octobre 2011), p. 2193.

Article 20:

« Aucune exigence ou recommandation faite pour un navire de pêche, conformément aux articles 15 ou 17 ci-dessus ne doit être de nature à porter atteinte à la sécurité de la navigation ou aux conditions réglementaires relatives au bien-être des équipages à bord dudit navire.

Pour ce faire, il doit être adjoint, dans les commissions de visite de mise en service des navires de pêche, les commissions annuelles de sécurité des navires de pêche et, le cas échéant, les commissions de recours:

– un représentant du service compétent conformément au décret précité n° 2-94-858 du 18 chaabane 1415 (20 janvier 1995);
– un vétérinaire de l'ONSSA pour donner l'avis sanitaire visé à l'article 2 de la loi précitée n° 25-08.»

3 Conditions for Placing Food and Feed Products on the Market

In accordance with the regulations, in particular law 28-07 relating to the health safety of food products, traceability is the ability to trace, through the food chain, the path of a primary product, a food product, of an animal feed, or an animal producer of primary products or food products, or of a substance intended to be incorporated or likely to be incorporated into a food product or animal feed.[4]

The new decree setting the conditions and modalities of labeling of food products provides for the making of two implementing decrees with the aim, of course, of responding to the concerns of professionals regarding the problems of labeling imported food products.[5]

The first decree, provided for in Article 8 of the abovementioned decree, concerns the exemption from the use of the Arabic language for certain products imported or intended for a particular clientele and certain drinks produced locally.

The second decree, stipulated in Article 30 of the decree, defines the forms and methods by which conformity of labels will be granted on imported products that, for

[4] Voir article 48 du décret n° 2-10-473, précité.

Article 48:

« Afin de garantir qu'un produit primaire, un produit alimentaire ou un aliment pour animaux importé en vue de sa mise sur le marché national est sans danger pour la vie ou la santé humaine ou animale conformément aux dispositions de l'article 4 de la loi précitée n° 28-07, l'importateur dudit produit ou aliment doit, préalablement à son importation, s'assurer que le produit ou l'aliment:

- provient d'un pays, d'une zone ou d'une région non soumise à des restrictions sanitaires ou phytosanitaires;
- répond aux exigences d'hygiène et de salubrité prévues par le présent décret et autres réglementations spécifiques au produit ou aliment;
- est issu d'un établissement ou d'une entreprise ayant mis en place un système d'autocontrôle HACCP ou un système équivalent;
- est accompagné de documents ou autres certificats exigés par une réglementation spécifique au produit ou aliment délivré par l'autorité compétente du pays d'exportation et attestant, notamment, qu'il est conforme à la législation en vigueur et sans danger pour la vie ou la santé humaine ou animale.

L'importateur doit disposer d'un plan de rappel lui permettant, en cas d'alerte sanitaire portant sur le produit ou l'aliment pour animaux qu'il a importé, de rappeler celui-ci après son admission sur le territoire national. »

[5] Voir article 4 du décret n° 2-10-473, précité.

Article 4:

«En application de l'article 5 de la loi précitée n° 28-07, sont soumis, avant leur mise en exploitation:

1) à l'agrément sur le plan sanitaire: les établissements et les entreprises du secteur alimentaire et du secteur de l'alimentation animale dont les activités entrent dans les catégories figurant sur la liste annexée au présent décret;

à l'autorisation sur le plan sanitaire: les établissements et les entreprises du secteur alimentaire et du secteur de l'alimentation animale autres que ceux prévus au 1) ci-dessus. »

technical or commercial reasons, cannot be marked under certain provisions of the decree.

It should be noted that these two draft decrees are being prepared at the level of ONSSA (Office National de Sécurité Sanitaire des Produits Alimentaires). Before publication, they will be subject to broad consultation with all of the operators concerned. Thus, Law 28-07 establishes the obligation to set up, by operators of the agrifood sector, traceability at all stages of the food chain. Indeed, operators of the agrifood sector must name any establishment to which they have supplied or transferred as well as any person who supplied or transferred to them a primary product, a food product, an animal feed, or an animal producer of products. Primary products, food, or any substance intended to be incorporated into primary products, food products, or animal feed.[6]

4 Competence, Investigation, and Observation of Infringements

According to Article 21 of the said law, "Authorized agents under the authority of the National Office for Food Safety[7] are responsible for the investigation and detection of infringements of the provisions of this Law and the texts adopted for its application, subject to the powers granted by law to the officers of the legal police

[6] Voir article 17 du décret n° 2–10-473, précité.

Article 17:

« Si, à l'occasion des visites sanitaires régulières, une ou plusieurs non-conformités ou insuffisances sont constatées, l'autorisation ou l'agrément sur le plan sanitaire peut être suspendu conformément au deuxième alinéa de l'article 7 de la loi précitée n° 28-07.

La décision de suspension de l'autorisation ou de l'agrément, selon le cas, mentionne les non-conformités ou insuffisances constatées avec des recommandations de mise en conformité ainsi que le délai, qui ne peut être supérieur à six mois, dans lequel l'exploitant doit remédier aux dites non- conformités ou insuffisances.

A l'issue de ce délai, s'il n'a pas été remédié aux non-conformités ou insuffisances constatées, l'autorisation ou l'agrément est retiré. Dans le cas contraire, il est mis fin à la mesure de suspension. »

[7] Voir article 37 du décret n° 2-10-473, précité.

Article 37:

« Les exploitants des établissements et entreprises du secteur de l'alimentation animale doivent veiller à ce que les différentes étapes de la production soient exécutées selon des procédures et instructions écrites préétablies visant à définir, à vérifier et à maîtriser les points critiques dans le processus de fabrication.

A cet effet:

1. des mesures à caractère technique ou organisationnel doivent être prises pour éviter ou limiter la contamination croisée et les erreurs;
2. des moyens suffisants et appropriés doivent être mis en place pour effectuer des vérifications au cours de la fabrication;

and other public authorities. The mandated veterinarians[8] may, under the control of the said office, be responsible for the same mission."

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3. une surveillance doit être assurée aux fins de détecter la présence dans les aliments pour animaux de substances interdites ou de contaminants et des stratégies de contrôle appropriées visant à réduire les risques au minimum doivent être mises en place;
4. les déchets et les matières indésirables pour l'alimentation animale doivent être isolés et identifiés. Notamment, toutes les matières contenant des quantités dangereuses de médicaments, vétérinaires ou de contaminants ou présentant d'autres risques, doivent être éliminées d'une manière appropriée et détruites;
5. la traçabilité des produits doit être assurée;
6. les documents relatifs aux matières premières utilisées pour la fabrication des aliments pour animaux doivent être conservés par le fabricant et tenus à la disposition des agents visés à l'article 21 de la loi précitée n° 28-07. ».

– Voir aussi article premier du décret n° 2-15-219 du 5 ramadan 1436 (22 juin 2015) pris pour l'application de l'article 21 de la loi n° 28-07 relative à la sécurité sanitaire des produits alimentaires; Bulletin Officiel n° 6378 du 29 ramadan 1436 (16 juillet 2015), p. 3208.
  Article premier:
  « Les agents habilités relevant de l'Office national de sécurité sanitaire des produits alimentaires (ONSSA) visés à l'article 21 de la loi susvisée n° 28-07 sont:

1. les fonctionnaires et agents de la répression des fraudes, les inspecteurs de la protection des végétaux, les vétérinaires inspecteurs et les techniciens de l'élevage, mentionnés à l'article 3 de la loi susvisée n° 25-08, détachés auprès de l'Office national de sécurité sanitaire des produits alimentaires (ONSSA);

2. les vétérinaires, les ingénieurs et les techniciens de l'ONSSA, titulaires, exerçant depuis une période minimale de deux (2) ans au sein de ses services centraux ou locaux.
   Pour exercer en qualité d'agent verbalisateur, les personnes susmentionnées doivent justifier avoir suivi une formation continue dans les domaines traités par la loi n° 28-07 précitée, selon le programme approuvé à cet effet par le directeur général de l'ONSSA. »

[8] Voir article 3 du décret n° 2-15-219, précité

Article 3:

« Les vétérinaires mandatés mentionnés à l'article 21 de la loi n° 28-07 précitée sont les vétérinaires exerçant à titre privé auxquels un mandant appelé « mandant d'inspection vétérinaire » est délivré par le directeur général de l'ONSSA, après avis de la commission prévue à l'article 4 ci-dessus, aux fins d'exécuter des missions dans les domaines de la santé animale et de la pharmacie vétérinaire couvertes par le mandant sanitaire dont ils disposent en vertu de la loi susvisée n° 21-80 ainsi que des missions de contrôle sanitaire des denrées animales, d'origine animale et des aliments pour animaux.

Pour bénéficier du mandant d'inspection vétérinaire prévu à l'alinéa ci-dessus, le demandeur doit remplir les conditions suivantes:

1. être régulièrement inscrit au tableau de l'Ordre national des vétérinaires;
2. disposer du mandant sanitaire délivré conformément aux dispositions du décret susvisé n° 2-82-541, en cours de validité;
3. ne pas avoir fait l'objet, au cours de sa carrière, d'une interdiction temporaire d'exercer, prononcée conformément aux dispo- sitions de l'article 17 de la loi précitée n° 21-80;
4. ne pas avoir fait l'objet d'une suspension du tableau de l'Ordre national des vétérinaires au cours des cinq années précédant la date de sa demande;
5. s'engager à ne pas divulguer les informations et les données auxquelles il a accès lors des missions qu'il effectue, en dehors de l'opérateur concerné et des services compétents de l'ONSSA.»

5 The Penalties

According to Articles 25 to 28 of the said law, the penalties incurred are:

Imprisonment of two (2) to six (6) months and a fine for 50,000 to 100,000 dirhams or one of these two penalties only, whoever:

- Has placed on the national market, imported or exported any primary product, food product or feed for animals that is dangerous for life or human or animal health;
- Has handled, treated, transformed, packaged, distributed, placed on the market or exported primary products, food products or feed from an establishment or undertaking without the authorization or the health authorization provided for in section 5 of this Law or to which the authorization or approval has been suspended or withdrawn;
- Failed to comply with the provisions of Law No. 28-07.

One is punished with a fine of 5000 to 20,000 dirhams, whoever:

- Has placed on the market or exported or imported a primary product or an unlabeled food product or feed in accordance with the conditions applicable to it in the application of this law and the texts adopted for its application or in the application of a specific legislative or regulatory text.
- Has not withdrawn any primary product, food product or animal feed from the national market within the time limit set by the competent authorities in accordance with Law No. 28-07.

One shall be punished by fifteen (15) days to six (6) months imprisonment and a forfeiture of 5000 to 100,000 dirhams or one of these two penalties only, whoever, by any means whatsoever, opposes the control provided for in Article 7 above or obstructs the investigation or detection of infringements of this Law, in violation of the provisions of Article 22 above.

6 The Control Procedure: ONSSA

Establishments and companies in the food sector of plant and plant products must get approval and/or authorization in terms of health by ONSSA in accordance with the provisions of the following laws and regulations:

The issue of health authorization or approval gives rise to allocate health approval or authorization number.

To be approved or authorized in terms of health, operators of food establishments and companies must complete the request for health approval and/or authorization and file it with the plant and plant products control department of the province where the establishment is located.

A file comprising an administrative part and a technical part must accompany each request for health approval or authorization.

The procedures for issuing, suspending, and withdrawing health approval and authorization are supported in the procedural code relating to the granting, suspension, and withdrawal of health approvals and authorizations.

7 Conditions for Placing Food Products and Animal Feeds on the Market

- Fix of the hygienic conditions applicable to the transport of food products and animal feed.
- Establish additional and specific provisions relating to the transport of products which may or may not deteriorate at ambient temperatures.
- Establish specific provisions for certain means of transport for food products or animal feed products.
- Establish additional provisions applicable to the transport of certain perishable food products.
- Repeal of the decree of the Minister of Agriculture, Rural Development and Marine Fisheries No. 938-99 of 29 safar 1420 (June 14, 1999) setting the conditions and conditions for maximum temperatures for the transport of perishable goods.
- Ensure that food products and animal feed placed on the market which are intended for export meet the requirements of this law and do not present any danger to life or human or animal health.
- Apply and maintain in establishments or companies a self-monitoring program or follow a guide to good health practices approved by the competent authorities.
- These companies must record all the procedures decided within the framework that execute the measures provided for in documents which must be kept for a minimum period of 5 years, from the date of their establishment, and which must be presented at any requisition agents provided for in Article 21 of this law.
- Inform the competent authorities immediately when a primary product, food product, or animal feed does not fulfill the conditions for qualifying as a safe product, in accordance with the provisions of this law, which takes all right measures to impose restrictions on its placing on the national market, to demand its withdrawal or to prohibit its export.
- The competent authorities, in accordance with the provisions of Articles 23 and 24 of this law, proceed to seize or consign it with a view to subjecting it to the necessary investigations to ensure its health security if the animal, the product, the food, element or additive present or may pose a danger to human or animal health.
- Recall and process the shipment in one or more places, with the aim of checking all the elements that make up the said batch, if the animal, product, food, element, or the additive is part of a lot.

8 The Animals' Marking and the Traceability of Materials, Primary Products, Food Products, and Animal Feed

- It is intended to establish traceability at all stages of the food chain of materials, primary products, food products, animal feed, food-producing animals, and any substance for inclusion or likely to be incorporated into a primary product, a food product, or in animal feed.
- The issuance of the declaration to the competent authorities by all operators or professionals who work in livestock breeding and which aims exclusively for human consumption in order to register their exploitation in the forms and methods fixed by regulatory means.
- Maintain or cause to be carried out the marking by the keepers of animals whose production is intended for human consumption of their animals born on their farm or acquired without having been marked by the original keeper.
- Animal marking procedures as well as identification marks and the affixing of said marks.
- The marking information to be included in the above-mentioned breeding register as well as the procedures for establishing said register and the conditions for its keeping.
- The provision of a register kept at the places of production of said products on which are recorded the factors of production such as chemical and organic materials used for the maintenance and management of the cultivation of the aforementioned products.

9 Consumer Information[9]

- The necessity to provide the marks for any food product and any animal food that is put or must be placed on the national market or intended for export or imported in accordance with the instructions applied to it under the provisions of the present law.
- The product must be labeled in a way that will allow the final consumer to become aware of its properties.
- The identification card must contain the founding elements, characteristics, and forms of signs and inscriptions of the product, while respecting the conditions and methods of affixing them, and they shall be determined by regulatory means.
- When labels for primary products, food products, and animal feed are recognized as incompatible, producers or those responsible for putting them on the market must withdraw them within a period to be determined by the competent authorities.

[9]Dahir n° 1-11-03 du 14 rabii I 1432 (18 février 2011) portant promulgation de la loi n° 31-08 édictant des mesures de protection du consommateurki

10 Competence, Research, and Finding of Offenses

Approved agents subject to the authority of the National Food Safety Office are responsible for researching and establishing violations of the provisions of this law, such as:

- Technical or organizational measures must be taken to avoid or reduce cross-contamination and errors.
- Sufficient and appropriate means must be put in place to carry out inspections during the manufacturing process.
- Monitoring should be carried out to detect the presence of banned substances or contaminants in the feed, and appropriate control strategies should be put in place aimed at minimizing risks.
- Unwanted residues and materials for animal feed should be isolated and identified. In particular, all materials containing dangerous quantities of veterinary drugs or contaminants or which pose other hazards must be disposed of in an appropriate manner and destroyed.
- Product traceability must be guaranteed.
- The manufacturer must keep the documents related to the raw materials used in the manufacture of feed, and keep them at the disposal of the agents referred to in Article 21 of the aforementioned Law No.28.07.

The approved agents mentioned in Article 21 above can make reservations or dispatch until the results of controls are issued:

- Products, food products, or animal feed likely to present a danger to human or animal health.
- Products, food products, or animal feed likely to be adulterated, corrupt, toxic, or expired.
- Products, foodstuffs, or animal feed likely to be unfit for human or animal consumption objects or apparatus which can be used to carry out falsifications.
- The deposit measure cannot exceed a duration of 20 days.

References

Decree n ° 2-14-268 of January 29, 2015 relating to the quality and health safety of olive oils and olive-pomace oils marketed

Decree No. 2-13-711 of March 4, 2015 relating to the quality and safety of marketed tea

Order of the Minister of Agriculture and Maritime Fisheries N ° 244-13 of 4 rabii 1 1434 (January 16, 2013) relating to the authorization and approval in terms of health of establishments and companies in the sector of the animal feed and food industry other than retail and catering

Decree No. 2-15-306 of 6 Joumada I1437 (February 15, 2016) relating to the quality and safety of juices and concentrates of fruit and vegetable juices and fruit nectars marketed

Decree No. 2-10-473 issued for the application of certain provisions of Law No. 28-07 relating to the safety of food products

Dahir n ° 1-–11-03 of 14 rabii I 1432 (February 18, 2011) promulgating Law n ° 31-08 enacting consumer protection measures

Electrochemical Sensors for Food Quality and Safety

Abdessamad Tounsi, Laila Midhat, Ahlam El Ghazali, Elmehdi Ouatiki, and Mohammed El Idrissi

Abstract Today, food security has become a growing concern worldwide. In addition, the increase in the number of potentially harmful pollutants in the environment has created a need for the development of efficient analytical methods for their detection. To this end, electrochemical sensors are emerging as suitable analytical tools as they provide a low-cost and sensitive tool based on portable devices capable of rapidly detecting a range of analytes with high sensitivity and specificity. In addition, these sensors have special recognition capabilities for a wide range of molecules, with high stability under extreme experimental conditions. This chapter describes electrochemical sensors and reviews the progress of their use for the detection and determination of food contaminants, namely, heavy metals, unlawful additives, residues of pesticide and residues of veterinary drug, biotoxins and microbial pathogens. Future prospects and challenges are also discussed.

Keywords Food safety · Electrochemical sensors · Electrochemical technique · Detection

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1 Introduction

Despite ever-increasing production, food insecurity has regained ground in recent years and has become a growing public health problem. This is the case in all countries and especially in developing ones where the situation continues to worsen. The globalization of food trade has tripled the volume of trade over the last 20 years. This has favored the origin of raw materials and ingredients from distant countries with less or no analysis and control structures, which today makes it very complicated to guarantee the safety, quality and traceability of food (Hamburg 2011). Thus, the food industry is exposed to risks of contamination or fraud, which may even endanger the health of the consumer as was the case of the fraud committed in some European countries in 2013. Undeclared or incorrectly declared horsemeat, in some cases up to 100% meat content, is found in meat products advertised as containing beef. Other undeclared meats, such as pork, have also been included in a smaller number of products.

Much of this complexity is due to this globalization and the movement of food and related raw materials around the world, which leads to episodes of contamination that are also globalized. In addition, many products contain multiple, processed ingredients, which are often shipped from different parts of the world, and share common storage space and production lines. An additional difficulty is the ban on chemical and biological products (pesticides, antibiotics, growth promoters, mycotoxins, phycotoxins, environmental contaminants and heavy metals) that are illegally introduced into food production and endanger food safety. The presence of these elements in food chain generates many food-borne illnesses caused by microbial pathogens, biotoxins and chemical pollutants.

The use of chemical pesticides in food production and storage results in the presence of hazardous residues, especially heavy metals. They can contaminate food products through soil, water or materials in contact with them. Their presence and persistence cause serious illness. The use of antibiotics and growth promoters for pets to prevent or stimulate their growth is also a significant problem. It is therefore very urgent to react to this problem, first by identifying the chemical or biological agents that are causing the problem.

In this context, modern analytical methods are an indispensable tool for the detection and quantification of a wide range of elements in food products. The detection and quantification of these elements are generally conducted by using chromatographic methods like High-Performance Liquid Chromatography (HPLC) (Armutcu et al. 2012), Gas Chromatography (GC) (Nolvachai et al. 2017), Liquid Chromatography-Mass Spectrometry (LC-MS) (Malik et al. 2010) and Gas Chromatography-Mass Spectrometry (GC-MS) (Wang et al. 2018) and by immunological detection methods such as the lateral flow immunoassay (Raeisossadati et al. 2016), the enzyme-linked immunosorbent assay (ELISA) (Ma et al. 2018) and hybridization chain reaction (HCR) (Yu et al. 2018). These methods are relatively sensitive and specific, but they are costly, laborious and time-consuming and require

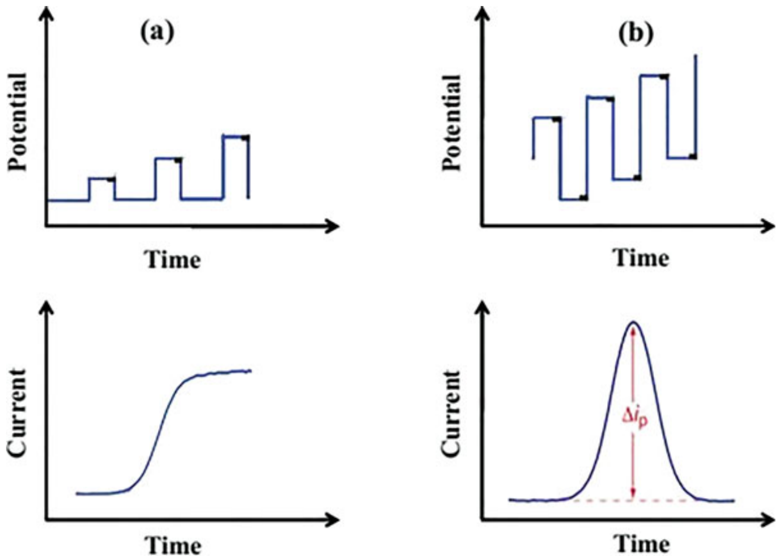

Fig. 1 Potential waveforms and their respective current response for (**a**) DPV and (**b**) SWV

qualified personnel (Thota and Ganesh 2016), thus necessitating the development of rapid, sensitive, accurate and on-line technologies for food safety detection.

Recently, biosensors have been the subject of a great deal of research and development work with the aim of offering simple, reliable and inexpensive systems. They have experienced considerable emergence due to their portability and simplicity, allowing the transformation of a biochemical signal into an electrical signal that can be easily exploited in situ. In addition, their numerous potential applications in food control make them the best alternatives to traditional analytical techniques that are quite complicated.

Linear scanning voltammetry (LSV) (Thota and Ganesh 2016), cyclic voltammetry (CV) (Yu et al. 2018), square wave voltammetry (SWV) (Li et al. 2015) and differential pulse voltammetry (DPV) (Gayathri et al. 2016) are techniques widely used in food control and food safety. Voltammetric techniques (DPV and SWV in particular) are commonly used because of their low detection limits and multiplex analysis. Both techniques consisting of applying amplitude potential pulses and respective electrical current peaks are observed for a given redox (Fig. 1). In DPV, short pulses with limited amplitude are superimposed on a linearly increasing DC ramp. By minimizing the capacitive current, the DPV technique has the highest sensitivity than the linear scanning methods. In addition, SWV is based on the combination of square wave amplitude modulation with a stepped ramp. The measured signal is the difference ΔiP between the measured currents, at the end of each pulse going up and down the square wave. SWV has the main advantage of varying the potential at much higher speeds, and thus allows the capacitive current to be minimized and subsequently the sensitivity is increased. The peak current values measured using the DPV and SWV methods are directly proportional to the concentrations of the elements to be quantitatively measured. Another important method of electrochemical analysis used in conjunction with biosensors is amperometry in which a constant potential is imposed on the working electrode whose faradic current is measured as a function of time. In order to achieve high values of the signal-to-noise ratio, the electric current is integrated over comparatively longer time intervals. Chronoamperometry is another important time-dependent electrochemical analysis method where a rectangular potential is applied to the working electrode. In response, the electrode current due to the diffusion of an analyte from the bulk solution to the sensor surface is measured as a function of time. The time dependence of the current for the diffusion-controlled process occurring at an electrode is measured using chronoamperometry. As with DPV and SWV, the recorded current is directly proportional to the concentration of the analyte (Bard and Faulkner 2001). Chronoamperometry is a highly sensitive electrochemical technique without analyte or bioreceptor labeling and has been applied in many studies in parallel or independently with other voltamperometric techniques such as CV.

Electrochemical sensors can be used as a quality and food safety control device. This chapter gives a description of electrochemical sensors and their use for food quality and safety. Firstly, we described some electrochemical sensors applied for quality control and food safety. Secondly, we summarized the sensor applications for the determination of food contaminants like heavy metals, unlawful additives, residues of pesticide, and residues of veterinary drug, biotoxins and microbial pathogens.

2 Biosensors

Modern electrochemistry provides powerful analytical techniques that are the sensors providing an instrumentally simple, miniaturized and inexpensive tool. These electrochemical sensors are based on portable devices capable of rapidly detecting a set of analytes with high sensitivity and specificity in complex matrices with minimal sample preparation (Yu et al. 2018).

2.1 Biosensor Principle

A biosensor is an integrated device providing specific quantitative or semiquantitative information through a biologically based recognition element in direct contact with a transducer element. The biosensor concept includes any measuring device defined by a pair of selective biological ligands linked to a transducer that transforms a biochemical phenomenon into a measurable signal (Thévenot et al. 2001).

The operating principle of a biosensor is shown in Fig. 2. The bioreceptor, which is a selective biological element (antibodies, enzymes, cells, DNA, cell organelles,

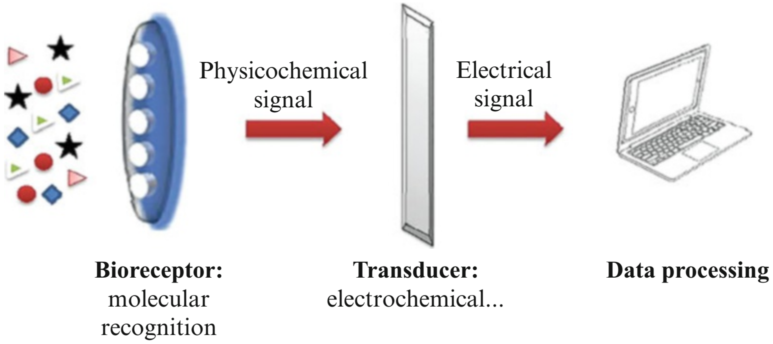

Fig. 2 Scheme of a biosensor

tissues...), catalyzes biochemical reactions or interferes with complementary structures, allowing changes in physical or chemical properties to be transformed into electrical signals that can be measured by the transducer. These signals will then be amplified and processed (Dupont 2005).

2.2 *Classification of Biosensors*

Biosensors can be classified by i) type of molecular recognition (bioreceptor): enzymatic biosensors (with an enzyme as bioreceptor), immunological biosensors, microbial biosensors, etc.; ii) type of associated transducer: electrochemical biosensors, optical biosensors and calorimetric biosensors and (iii) species detected: Biosensors can also be classified according to the reactions they allow to follow directly an analyte or a biological activity, or indirectly through, for example, the monitoring of an inhibition of catalytic activity by toxins or heavy metals (El Hassani 2018).

2.3 *Recognition Elements of a Biosensor*

Biosensor technology is based on biological recognition elements called bioreceptors, which are defined as molecular entities using a specific biochemical recognition mechanism (Perumal and Hashim 2014). The bioreceptor translates the molecular detection associated or not with the transformation of the analyte. This modification of the species present in the sample is generally determined via an active molecule: enzyme, antibody, DNA or microorganism. The active molecule can be immobilized near the surface of the transducer by physisorption, chemosorption, or trapping in an inert membrane. It is important to note that the bioreceptor provides high specificity and sensitivity for the analyte, resulting in a

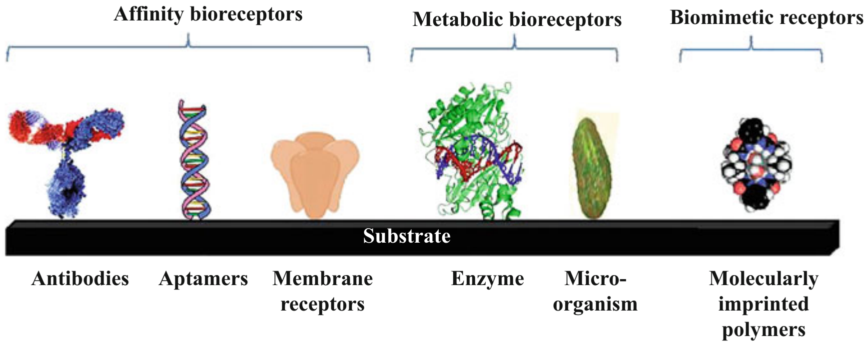

Fig. 3 Different types of bioreceptors

rapid response. As shown in Fig. 3, bioreceptors are classified according to their type of activity into affinity bioreceptors that normally bind to the analyte without altering it, metabolic bioreceptors that have catalytic activity and biomimetic receptors. Several parameters such as stability, specificity, lifetime and ease of use are key elements in the choice of bioreceptors.

2.4 Different Modes of Transduction

It is the physical element that is used to exploit the biochemical modifications of the bioreceptor substrate to transform them into an electrical signal that can be amplified, displayed and saved. The transducer converts the signal from a molecular recognition act either directly or through a chemical mediator. It should be noted that the choice of transducer depends not only on the type of reaction and the substances released or consumed but also on the application of the biosensor (Mai 2004).

The nature of the transducer often serves as a basis for the classification of the different biosensors. Numerous transducers have been used to develop biosensors, including optical, thermal, mechanical and electrochemical transducers.

2.5 Characteristics of Biosensors

To evaluate sensor and its analytical qualities, different characteristics should take them into account. The most used are:

***Selectivity*:** This is the ability of the biosensor to distinguish between different substrates. It is a parameter that depends mainly on the biological component, although sometimes the choice of transducer can contribute to selectivity.

Sensitivity: This parameter corresponds to the ratio between the increase in the response of the sensor and the corresponding variation in the quantity to be measured.

Reproducibility: This is one of the most important parameters. It indicates the capacity of the biosensor to give very similar responses for repeated measurements of the same quantity of the quantity to be measured.

Accuracy: This is the agreement between the result of the measurement and the true value of the measured quantity and the deviation is called the absolute error.

Detection limit: It is the smallest value of the quantity to be measured that can be detected by the biosensor in a way significantly different from the background noise.

Hysteresis: It is the response to a signal that depends on the previous sequence (undesirable properties).

2.6 Influence Quantities

Depending on their nature and their importance, the influence quantities are extrinsic variables which can disturb the sensor, therefore inducing errors which can act on the output signal. The main influencing variables are:

Temperature: Which modifies the electrical, mechanical and dimensional characteristics of the sensor components.

Pressure: Acceleration and vibration, which can create deformations and stresses in certain components of the sensor that alter the response.

Humidity: To which certain electrical properties such as the dielectric constant or resistivity can be sensitive and which can degrade the electrical insulation between sensor components or between the sensor and its environment.

Variable or static magnetic fields: The former create electromotive force of induction, which is superimposed on the useful signal, and the latter can modify an electrical property, the supply voltage.

3 Food Contaminations

3.1 Heavy Metals

The term "heavy metals" (HM) is an ambiguous word, and its definition varies from one source to another (Nies 1999; Gadd 1992). The use of this term does not refer to a given concentration range, but to a physical property which is density. This term refers to natural metallic elements, metals or, in some cases, metalloids, characterized by a density greater than 5 g.cm^{-3}.

By polluting the global biosphere, nonabsorbable heavy metals with a high accumulation potential in the environment as well as in different organs and parts of our body cause many health problems (Gong et al. 2016; Lu et al. 2018). On the one hand, some nonessential metals such as cadmium, lead, mercury and arsenic are toxic even at very low concentrations (Bansod et al. 2017; Gumpu et al. 2015; Tsai et al. 2018). On the other hand, essential metals can also become hazardous at high concentrations such as zinc, copper, and iron. Therefore, it is necessary to be able to identify metallic pollutants present in the environment and to quantify them at trace and ultra-trace levels. To face the new challenges of analytical problems, there is an urgent need to perform several analyses simultaneously and rapidly in the same samples, using reliable, sensitive and reproducible analytical methods that are highly selective and, if possible, inexpensive.

Electrochemical techniques offer the advantage of being fast, sensitive and easy to implement (Wang and Anal 1990; Galus 1994). In this context, electrochemical methods have many advantages over spectroscopic methods, as the equipment is less expensive and measurements can be performed directly on site (Galus 1994; Afkhami et al. 2013).

For a number of years, very low concentrations of HMs have been measured over the wide range of cathode potentials using a combination of mercury anodic redissolution voltammetry (ASV) and modified electrodes (Wang 2007; Barek et al. 2001; Tercier et al. 1998; Fischer and Berg 1999). Many researchers (N.F.T 1986; Cordon et al. 2002) have detected trace metals on the mercury electrode surface, based on the complexation of these ions with diacetyldioxime in solution. Promising results have been obtained by this electrode but the samples are contaminated by diacetyldioxime. In addition, mercury-containing equipment can be grounded and mishandled and the resulting mercury vapor is a serious risk to the environment and human health (Svancara et al. 2010). As a result, various mercury-free electrodes have been developed in recent decades.

Baldwin (Tuzhi et al. 1994) was the first to use diacetyldioxime as a carbon paste electrode modifier for the determination of Ni(II) and Cu(I). Direct insertion of the modifier is the most widely used strategy for modifying carbon paste electrodes. Carbon paste is one of the most convenient materials for the preparation of modified electrodes (Baird 1995). Mousavi et al. modified the carbon paste electrode with 1,4-bis(prop-2-enyloxy)-9,10-anthraquinone to detect lead using square wave anodic redissolution voltammetry (SARV). Further work on the determination of the same metal was carried out by modifying the carbon paste electrode (Degfa et al. 1999; Schreurs and Barendrecht 1984).

For a practical application, an increasing number of electrochemical sensors using screen-printed carbon electrodes (SPCE) have been developed for the detection of traces of heavy metals in food safety because they are inexpensive, portable and easy to mass produce (Yao et al. 2019; Jian et al. 2018).

3.2 Unlawful Additives

Food adulteration and fraud are as old as food manufacturing. Adulteration with a specifically economic motivation has raised public awareness because of the serious public health risks it can cause. Intentional food fraud and the goal of financial gain are mainly characterized by the noncompliance with food legislation and/or the misleading of the consumer. The addition of inedible substances and the abuse of food additives such as Sudan I, melamine and clenbuterol are the main problems affecting food safety and can pose a great threat to human health (Martins et al. 2019). In addition to compliance with national legislation, international standards, and other guidelines, consumer (Johnson 2014) protection, food safety and food quality are guaranteed in an important way through food authentication.

With the globalization of the food supply, the problem of food fraud has become more sinister with an increased destructive potential manifested by an increase in the number of food recalls per year and a recent series of incidents of adulteration that have resulted in serious economic and health costs (Kearney 2010). The multitude of sources from which many product ingredients originate makes it difficult to detect and trace the origin of unintentional contamination and especially intentional product fraud and related food safety issues.

In the food industry, therefore, authenticity has become a major concern at all levels of the production and distribution process, from raw materials to finished products. Quality standards have been introduced to specify the main components of each product, and their authentication is necessary to avoid unfair competition that can destabilize the market and disrupt the economy.

Faced with this imperative of consumer protection and food safety, food researchers are committed to the research and development of rapid and accurate analytical techniques for food adulteration and fraud. For the detection of specific chemical contaminants and illegal additives, various approaches using nanomaterial-based biosensors have been developed (Zhang et al. 2017; Yan et al. 2016; Wang et al. 2015). A modified reduced graphene oxide (RGO) electrode decorated with gold nanoparticles (AuNPs) has been developed (Li et al. 2015) and applied for the detection of Sudan I in ketchup sauce. A wide linear detection range of Sudan I from 0.01 to 70 μmol.L^{-1} and a low detection limit of 1.0 nmol.L^{-1} were obtained with this biosensor under optimal conditions. A sensitive and selective electrochemical sensor consisting of a nanohybrid modified glassy carbon electrode MIL-53 @ XC-72 (GCE) was also designed to determine melamine with a linear range of 0.04 to 10 μmol.L^{-1} and a limit of detection (LOD) of 0.005 μmol.L^{-1} (Zhang et al. 2016). The use of this.

electrochemical biosensor for the determination of melamine in liquid milk has been very stable, highly selective and a good reproducibility of measurements with excellent recovery rates has also been achieved. For a simultaneous determination of both vanillin as well as caffeine (Jiang et al. 2014), an electrochemical sensor using materials combining nitrogen-doped carbon nanotubes (NCNT) and nitrogen-doped graphene (NGR) was also applied. Electrochemical sensors for sunshine yellow and many other food additives determination have also been developed (Yin et al. 2018; Shah et al. 2018).

3.3 Residues of Pesticide

Pesticides, namely fungicides, herbicides, molluscicides and insecticides, are largely used to increase agricultural productivity by controlling pests that can destroy or reduce food production (Nsibande and Forbes 2016; Kumar et al. 2015).

The use of pesticides in agriculture is becoming increasingly important. However, their intensive use, especially organophosphates and N-methyl carbamates, can lead to their occurrence as residues in crops, livestock and poultry products. Following their penetration into the food chain, contamination and toxicity based on the inhibition of acetylcholinesterase (AChE) can cause serious illnesses, including bone marrow disorders, carcinogenicity, cytogenic effects, sterility, neurological diseases and immunological and respiratory problems. Therefore, the detection of pesticide residues is very important for food control and food safety (London et al. 1998).

To date, many methods especially chromatographic techniques are classically applied for the detection of pesticide residues in food samples. For this purpose, electrochemical methods based on a variety of electrochemical biosensors have been described by several researchers. These biosensors make it possible to elucidate the processes and mechanisms of the redox reaction of pesticides and their residues (Chauhan and Pundir 2012) using mainly enzymes and entire cells as elements of biological reconnaissance, and to a limited extent DNA or antibodies (Lagarde and Jaffrezic-Renault 2011; Sassolas et al. 2012). These biosensors are not only sensitive, reliable and fast, but can also be easily miniaturized and integrated with other analytical techniques (Grieshaber et al. 2008; Rassaei et al. 2011).

A magneto-actuated enzyme-free electrochemical biosensor based on magnetic molecularly imprinted polymer has been developed and applied for the detection of methyl parathion in fish samples. Outstanding analytical performance was achieved with recovery values ranging from 89.4% to 94.7% and a detection limit as low as 1.22×10^{-6} mg.L^{-1} (Hassan et al. 2018).

In addition, a biosensor combining a modified electrode with reduced graphene oxide and acetylcholinesterase (AChE) was used for rapid detection of carbaryl in tomato samples (Da Silva et al. 2018). As the concentration of acetylthiocholine chloride increased the electrochemical response increased and decreased in the presence of AChE-inhibiting OPs. The response to inhibition of the thiocholine oxidation process was linear for carbaryl concentrations between 10 and 50 nmol. L^{-1} and between 0.2 and 1.0 mol.L^{-1}. Organophosphorus hydrolase enzymes used as catalysts for the hydrolysis of organophosphorus (OPs) pesticides give a high turnover rate compared to AChE, and are potentially reusable and therefore suitable for permanent OPs control (Stoytcheva et al. 2016; Sahin et al. 2017).

3.4 Veterinary Drug Residues

Veterinary medicines, especially antiparasitic and antimicrobial drugs, and growth promoters, are routinely administered to animals in feed or drinking water for disease prevention and treatment, feed efficiency and animal growth promotion (Wu et al. 2016). However, the possible presence of veterinary drugs in foods of animal origin and the extensive use of antibiotics that may lead to the development of bacterial resistance are the major food safety issues that raise serious concerns about consumer health protection. On the basis of food safety (Lan et al. 2017) (European Commission, 1996), many countries have defined maximum residue limits (MRLs) for veterinary drugs in various foodstuffs of animal origin such as dairy and meat products entering the human food chain.

In Europe, and since 1996, the veterinary drug residue survey has been ruled by Council Directive 96/23/EC (European Commission, 1996) which prohibits the use of antibiotics as growth promoters. It is therefore very important to develop rapid and accurate methods to detect residues of veterinary drugs in general in foods of animal origin. Electrochemical sensors have attracted considerable attention in the field of control and food safety (Kimmel et al. 2012; Zhu et al. 2018). Developments in the field of biosensors for the bioanalytical detection of antibiotics in food, namely ß-lactams, aminoglycosides, quinolones, ß-lactam antibiotics, macrolides, fenicols, tetracyclines and sulfonamides have been described by several research groups (Babington et al. 2012; Huet *et al.* 2010). Lin et al. (2013) developed a CNT-modified hybrid electrode for the simultaneous determination of toxic salbutamol and ractopamine in pork samples with mean recoveries of 97.1% and 98.7%, respectively.

Further amperometric biosensors have been developed for the targeted measurement of antibiotic β-lactam residues in milk, which was achieved by a direct competitive test employing a tracer with horseradish peroxidase (HRP) for enzyme labeling (Conzuelo et al. 2013). The aim of this new strategy is to design affinity biosensors using a recombinant bacterial penicillin-binding protein (PBP) labeled with an N-terminal hexahistidine tail immobilized on nitrilotriacetic acid (NTA)-modified SPCEs. The improved affinity sensor provided detection limits at low ppb levels of antibiotics tested in untreated milk samples. In addition, the biosensor showed an analysis time of approximately 30 minutes and good selectivity toward other antibiotic residues which are frequently detected in milk and milk products derived from its processing.

A simple, fast and highly sensitive homogeneous electrochemical biosensor for the measurement of ampicillin, using target-initiated T7 exonuclease assisted signal amplification, has been developed. This highly selective electrochemical biosensor has a very low detection limit of approximately 4.0 pM of ampicillin, proving its applicability in successfully determining the antibiotic in milk. In addition, the tedious and time-consuming steps of modifying electrodes could be avoided, rendering experimental procedures significantly more efficient for the detection of antibiotic residues in the field of food safety (Wang et al. 2016).

The majority of electrochemical biosensors proposed for the detection of antibiotics are immunosensors designed with or without nanomaterials. For those involving nanomaterials, there is a range of signal amplification strategies including combinations of antibodies with single constituents of graphene oxide (GO), carbon nanotubes (CNT), AuNPs, Au nanorods and magnetic nanoparticles (MNPs) (Cai et al. 2012; Gamella et al. 2013; Guo et al. 2015; Wu et al. 2012; Yang et al. 2011; Zang et al. 2013). For the detection of tetracycline by DPV, an aptasensor has been recently developed by combining multiwalled carbon nanotubes-chitosan (MWCNTs-CS) and chitosan-Prussian blue-graphene (CS-PB-GR) nanoparticles assembled on a glassy carbon electrode. The sensitivity and stability of the electrode were increased, and the LOD obtained was 5.6 pM.

For inexpensive, rapid, simple and sensitive electrochemical analysis of antibiotic residues in milk samples, a novel biosensor consisting of a paper-based immunosensor was proposed (Wu et al. 2012). In order to develop a sensitive biosensor with high electrical conductivity, the filter paper was immersed in the composite coating solution obtained by impregnating the well-dispersed SWNTs with neomycin antibodies. For neomycin concentrations between 0.2 and 125 ng. mL^{-1}, the collected chronoamperometric signal increased, and the LOD obtained was 0.04 ng.mL^{-1}, much lower than the European regulation for neomycin detection. The biosensor was used with success in the analysis of enriched milk specimens.

3.5 Biotoxins

Food biotoxins are regarded as natural compounds comprising panoply of molecules. They are produced by the metabolic processes of algae, fungi, bacteria or plants with deleterious impacts on humans or other vertebrates, at even very low quantities. Biological toxins are usually classified into three major groups: plant/bacterial toxins, algal toxins and mycotoxins.

Mycotoxins, which are of fungal origin, are toxic and chemically heterogeneous secondary metabolites. Currently, more than 400 different mycotoxins are recognized with a wide variety of chemical structures, physicochemical, and toxicological properties. The danger of mycotoxins to health is enormous because some mycotoxins are responsible for genetic disorders and the progression of carcinogenesis, while others have teratogenic, embryotoxic and allergenic effects (Marin et al. 2013).

In general, mycotoxins are easily detected in agricultural crops, dairy products and alcohols (Schenzel et al. 2012). Mycotoxins can be found in the human or animal body through the consumption of contaminated animals or food products such as alcoholic beverages, wheat, maize, barley, sugar cane, cottonseed, peanuts, rice, sugar beets, sorghum and hard cheese (Marín et al. 2018).

Mycotoxin contamination of agricultural crops can occur at different levels of the food chain from preharvest to storage or transport. Many countries have established strict regulations for the control of the toxicity of these molecules in foodstuffs and legislation for the control of their possible contamination has been put in place.

Several mycotoxins have recently been detected in food samples, including aflatoxins and ochratoxin A (OTA). The field of research for this type of mycotoxins using electrochemical biosensor techniques remains very active.

Mishra et al. 2015 have successfully used a simple and sensitive biosensor for the detection of OTA via covalent binding of OTA aptamers to SPEs. They obtained a linear detection range between 0.15 and 2.5 ng/mL. A number of other electrochemical biosensors have also been developed using antibody selectivity or a combination of stability and selectivity of aptamers for OTA determination (Vidal et al. 2013). Different approaches have been suggested to enhance the signal through the use of nanoparticles obtained from gold, iron and graphene. Another strategy using a combination of AuNPs and polymers for efficient OTA determination has been described (Evtugyn et al. 2013).

3.6 Microbial Pathogens

A pathogenic microorganism is any microorganism (virus, bacteria, protozoan, etc.) capable of causing disease in other organisms, humans or animals. Food-borne illnesses are usually the result of eating food which is contaminated with pathogens, namely fungi, bacteria, viruses and parasites or their toxins. These diseases have become a major public health problem around the world over the past 20 years. It has been reported that in 2005, 1.8 million people died from diarrheal diseases and a large proportion of these cases are attributed to contamination of food and drinking water (WHO Report, 2007) (Henson and Humphrey 2009). Approximately 90% of food-borne diseases are due to the contamination of food by pathogens such as Bacillus *cereus, Escherichia coli, Streptococcus, Salmonella typhimurium, Staphylococcus aureus*, etc.

Traditional methods of identifying bacteria generally consist of a variety of cultivation techniques and biochemical tests that usually take 2–4 days. Adequate monitoring technologies that can be performed within hours to prevent mortality and morbidity caused by outbreaks are therefore necessary (Cabral 2010). The complication of these tests and the long duration of their performance have led several research groups to develop other less time-consuming techniques such as ELISA and PCR. Nevertheless, their widespread implementation is excluded due to limitations including the precise design of primers, the requirement for a specific labeled secondary antibody and their inability to distinguish between spore viability (Mansfield and Forsythe 2001; Chen et al. 2000; Dwived and Jaykus 2011; Heyduk and Heyduk 2010).

Recently, numerous biosensors using electrochemical techniques (Majdinasab et al. 2017) for the detection of several bacteria and parasites have been reported. The electrochemical biosensor has become a sensitive technique for bacterial analysis due to its many benefits such as fast reaction time, low price and compactness. In addition, the detection time is significantly improved and some newer methods require as little as 10 minutes. Sensitive detection limits for microbes have also been improved by incorporating nanomaterials such as AuNPs, CNT and GO, or by amplifying enzyme- labeled probes. Recently, Ma et al. (2014) reported a method based on electrochemical impedance spectroscopy for the detection of the pathogen *Salmonella typhimurium* in swines. The analysis using a biosensor based on a glassy carbon electrode modified with AuNPs and GO this method was found to be specific and rapid, and a limit of detection (LOD) of 3 CFU.mL^{-1} was obtained.

In addition, Zelada-Guillén et al. developed a potentiometric electrochemical sensor for the detection of Staphylococcus aureus using a single-walled carbon nanotube array (SWCNT) to reach 800 CFU.mL^{-1} in swine skin (Zelada-Guillén et al. 2012).

In addition to these detection methods, other newly described have employed DNA-based biosensors for the analysis of food samples. In this context, a biosensor based on an AuNP-modified graphite pencil electrode has been developed for the detection of the pathogen Bacillus cereus in milk and infant formula with a limit of detection (LOD) of 10 CFU.mL^{-1} (Izadi et al. 2016). Ligaj et al. (2014) developed another glassy carbon biosensor modified with multiwalled carbon nanotubes (MWCNTs) containing an immobilized DNA probe for the determination of *Aeromonas hydrophila* in both fish and légumes.

An impedimetric biosensor based on the specific bacterial recognition by a particular aptamer has been successfully tested for the determination of *Salmonella spp.* This biosensor provided a detection range between 2.4 and 2.4 $\times$ 10^3 CFU. mL^{-1} and an LOD of 3 CFU.mL^{-1} (Ma et al. 2014).

For the rapid detection of *Salmonella typhimurium* in a spiked food sample, Sheikhzadeh et al. (2016) developed an impedimetric biosensor based on the aptamer-bearing poly [pyrrole-co-3-carboxyl-pyrrole]. *S. typhimurium* was selectively detected in the concentration range of 10^2 to 10^8 CFU.mL^{-1} with a limit of detection (LOD) of 3 CFU.mL^{-1}. Additional electrochemical biosensors have been developed for the multiplexed detection of pathogenic bacteria, including an AuNP- and MNP-based barcode biosensor in a chip with a screen-printed carbon electrode (Zhang et al. 2010). It has been shown that the detection limits of this sensor against *Salmonella Bacillus* and *Anthracis enteritis* are 0.5 ng.mL^{-1} and 50 pg.mL^{-1}, respectively. Similarly, Dou et al. developed an immunosensor based on carbon-screen printed low-density matrices coated with MWCNT/sodium aluminate/sodium carboxymethyl chitosan composite films and functionalized with HRP-labeled antibodies. This biosensor was able to detect *Escherichia coli* O157: H7 with an LOD of 3.47 $\times$ 10^3 CFU.mL^{-1} (Dou et al. 2013).

4 Conclusion

Quality control and food safety continue to be major and growing concerns in terms of consumer health, enhancing food safety and promoting international trade.

Food quality and safety control are multidisciplinary fields that benefit from input from the various fields of instrumentation, biology, agriculture, mathematics and statistics, computer science and food technology.

These electrochemical sensors for the detection of food contaminants are continuing to provide many advantages, including fast response, field usability, high sensitivity, high selectivity and on-line analysis.

In addition, the relatively low cost and greatly improved miniaturization of these electrochemical sensors can play a key role in food processing quality control, improving the quality and safety of food products. However, the stability of electrochemical sensors remains a bottleneck for their development of large-scale detection and determination of food contaminants and fraudulent additives. Despite these constraints, sensors for food monitoring and food safety have recently been commercialized with a satisfactory return on investment from users.

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Nutrigenomics and Transcriptomics for a Personalized Nutrition

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Abstract The field of nutrigenomics encompasses multiple approaches aimed at understanding the effects of diet and dietary components on growth, health, and disease development of living organisms, following multiple "omic" parameters. The major "omics" approaches include genomics, transcriptomics, proteomics, metabolomics, and the microbiome. Transcriptomics is most widely used for profiling living organisms' gene expression at a defined nutritional state, which helps provide the whole picture of how dietary interventions alter intracellular RNA transcripts. Two technologies have been developed to quantify the transcriptome: hybridization-based (Microarray) or sequence-based (RNA-seq). Two research approaches, namely a "mechanistic" and a "biomarker profiling," are discussed in nutritional transcriptomics. The mechanistic approach helps identify nutrient-related molecular and signaling pathways. The biomarker profiling approach's goal is the characterization of early biomarkers that are indicative of a phenotype or a disease state. In short, transcriptomics methods can be

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used for a better understanding of the genome-wide nutrient–gene relationship which enables accurate, tailor-made nutritional advice toward personalized nutrition.

Keywords Nutrigenomics · Omics · Transcriptomics · Microarray · RNA-seq · Mechanistic · Biomarkers · Nutrition System Biology · Personalized nutrition

1 Introduction

Nutrition research, in the past decade, shifted from focusing on epidemiology and physiology to molecular biology and genetics.[1] It was mainly due to the large number of genetic information that was made accessible, thanks to large genome projects, and drew attention to the importance of genes in human nutrition.[2] Diet was also linked to genetic predispositions that are considered major contributors in the mortality rate of various noncommunicable diseases such as cancer, type II diabetes, and cardiovascular diseases.[3] Nutrition researchers increasingly started to recognize that nutrients play an important role as dietary signals influencing the metabolic process of cells and playing an important role in controlling homeostasis[4] (Table 1). These factors led a step closer to following Hippocrates's advice who offered that, "Positive health requires a knowledge of man's primary constitution and the powers of various foods, both those natural to them and those resulting from human skill."

Nutrigenomics brings along additional dimensions, new terminology, novel experimental techniques, and a new approach to nutrition research, such as high-throughput technologies that enable the global study of gene expression in a cell or organism. The subtle change in genome-wide gene expression can now be measured by quantitative techniques such as high-density microarray that allow the study of the whole transcriptome.[5] Comparable progress is made in other "Omics" fields such as the analysis of the nutrition-relevant metabolome (Metabolomics)[6] and proteome (Proteomics).[7] The integration of these "omics" layers will allow the analysis of the whole systems' response to nutrients (Nutrition System Biology) toward personalized nutrition that can be translated into recommendations for achieving specific health for individuals.

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Table 1 The effect of nutrients on regulating transcription via transcription factors in humans

Nutrient	Effect on transcription	Publication
Vitamin E	δ-Tocotrienol, a bioactive vitamin E, targets zinc finger transcription factor EGR-1 (early growth response protein 1) in the human pancreatic cancer cell line via the induction in the expression of the proapoptotic protein Bcl-2-associated X protein (Bax).	Wang et al.[a]
	Increasing transcription of NOXA gene (Phorbol-12-myristate-13-acetate-induced protein 1) that serve for apoptosis in breast cancer cells resulting in a higher expression of the cell-cycle-related genes *Ccnb2* (G2/mitotic-specific cyclin-B2), *Cdc2* (cyclin-dependent kinase 1) and *Cdc6* (cell division control), putatively indicating the mechanism for the improved cell division capacity of T cells.	Wang et al.,[b] Han et al.[c]
Vitamin D	Moderate the differentiation process of myeloid progenitors into monocytes and granulocytes and enhance the capacity of macrophages and dendritic cells via the transcription factor VDR (vitamin D receptor).	Carlberg[d]
Selenium	Control the expression of many genes integrated in immunity, cardiovascularity and fertility via selenocysteine codon. It also plays a role in the thyroid hormone balance and is considered a therapeutic approach in cases of refractory hypothyroidism.	Lammi & Qu[e]
Retinoic acid	Stimulating *Runx2* (runt-related transcription factor 2) expression, and reducing the expression of the transcription factor *Sp7* and the WNT genes *cMyc* (proto-oncogene and encodes a nuclear phosphoprotein that plays a role in cell-cycle progression, apoptosis and cellular transformation), *Lef1* (lymphoid enhancer-binding factor 1), *Lrp5* (low-density lipoprotein receptor-related protein 5), *Lrp6* and *Wnt11* that is involved in ossification.	Roa et al.[f]
Leucine	A deprivation of leucine regulate GCN2 (general control Nonderepressible 2)/ eIF2α (eukaryotic initiation factor 2 alpha) /ATF4 (activating transcription factor 4) /FGF21 (fibroblast growth factor 21), reduce the energy intake and improve insulin sensitivity.	Haro et al.[g]
Carbohydrates	Binds to the carbohydrate-responsive element binding protein (ChREBP) and promotes the storage of sugars as triglycerides (TGs) by inducing the transcription of enzymes included in lipogenesis and the pentose pathway.	Haro et al.[h]

[a]Chen Wang et al., *EGR-1/Bax pathway plays a role in vitamin E δ-tocotrienol-induced apoptosis in pancreatic cancer cells*, 26 J. Nutr. Biochem. 797–807 (2015).
[b]Pei Wang et al., *Involvement of JNK/p73/NOXA in vitamin E analog-induced apoptosis of human breast cancer cells*, 47 Mol. Carcinog. 436–445 (2008).
[c]Sung Nim Han et al., *Age and Vitamin E-Induced Changes in Gene Expression Profiles of T Cells*, 177 J. Immunol. 6052–6061 (2006).
[d]Carsten Carlberg, *Nutrigenomics of Vitamin D*, 11 Nutrients 676 (2019).
[e]Mikko J. Lammi & Chengjuan Qu, *Selenium-Related Transcriptional Regulation of Gene Expression*, 19 Int. J. Mol. Sci. 2665 (2018).
[f]Laury A Roa et al., *Retinoic acid disrupts osteogenesis in pre-osteoblasts by down- regulating WNT signaling*, 116 Int. J. Biochem. Cell Biol. 105597 (2019).
[g]Diego Haro, Pedro F. Marrero & Joana Relat, *Nutritional Regulation of Gene Expression: Carbohydrate-, Fat- and Amino Acid-Dependent Modulation of Transcriptional Activity*, 20 Int. J. Mol. Sci. 1386 (2019).
[h]*Id.*

In this review on nutrigenomics, we will focus on the transcriptomics fields of the nutrition system biology approach and define the methods used to analyze cell and organism transcriptomes. The impact of nutrients and diet on the whole-genome gene expression will be described and its relation to health and disease will be discussed. The enabling of the genome-wide nutrient–gene relationship to tailor-made nutritional advice toward personalized nutrition will be projected.

2 What Is Nutrigenomics?

Nutrigenomics is the study of how specific genes are influenced by nutrition on a genome-wide scale. The concept of nutrigenomics is based on the premise that the human genome can be affected, either directly or indirectly, by food components altering genes expression and their products.[8] In nutrigenomics, nutrients, which are considered dietary signals, are detected by the cellular sensor system influencing gene and protein expression and, eventually, metabolite production.[9] A change in their expression pattern is viewed as dietary signatures.[10] Nutrigenomics seeks to study these dietary signatures to determine how nutrients regulate gene and protein expression and, subsequently, influence homeostasis.[11] The study of nutrigenomics and the changes in genes and proteins expression could be key to understanding the risk of diet-related diseases and ultimately moving to a personalized approach to nutrition.

3 Gene–Nutrient Interaction

Nutrient–gene interaction can occur in three ways.[12] Direct interaction occurs when nutrients behave as transcription factors that can bind to DNA and modify gene expression. In epigenetic interaction, the structure of the DNA is altered by nutrients causing a chronic alteration in gene expression. Lastly, genetic variations such as Single-Nucleotide Polymorphisms (SNPs) can alter functionality of genes.[13] SNPs are the most common form of polymorphism and there is approximately 1 SNP per 1.91 kilobases of human DNA sequences.[14] An example of SNPs is Phenylketonuria

[8] Elaine Trujillo, Cindy Davis & John Milner, *Nutrigenomics, Proteomics, Metabolomics, and the Practice of Dietetics*, 106 J. Am. Diet. Assoc. 403–413 (2006).

[9] John C. Mathers, *Nutrigenomics in the modern era*, 76 Proc. Nutr. Soc. 265–275 (2017).

[10] Müller and Kersten, *supra* note 1.

[11] V. S. Neeha & Priyamvadah Kinth, *Nutrigenomics research: a review*, 50 J. Food Sci. Technol. 415–428 (2013).

[12] R. A. Siddique et al., *Nutrigenomics: Nutrient-Gene Interactions*, 25 Food Rev. Int. 326–345 (2009).

[13] *Id.*

[14] Aravinda Chakravarti, *. . .to a future of genetic medicine*, 409 Nature 822–823 (2001).

where patients should avoid phenylalanine-rich food. In this disorder, phenylalanine is not metabolized to tyrosine. Increased levels of blood phenylalanine cause irreversible brain damage. Hence, a phenylalanine-restricted diet is able to provide enough protein–energy, and other nutrients for ideal growth and brain development. It also includes a tyrosine supplement to preserve the phenylalanine plasma concentration in a healthy range of 2–6 mg/dl.[15] Galactosemia is another inherited genetic deficiency in one of the enzymes responsible for the metabolism of galactose. Another example of gene–nutrient interaction is dietary cholesterol that inhibits the transcription of β-hydroxy-β-methyl-glutaryl-CoA reductase gene.[16] By decreasing mRNA for lipogenic enzymes, dietary polyunsaturated fatty acids repress mRNA production of fatty acid synthesis in hepatocytes, and this process is dependent on the degree of unsaturation of fatty acids.[17] Another study by Janine Giovanella et al. demonstrated that in the increase in sodium and magnesium consumption, a higher level of systolic blood pressure (SBP) was detected. Individuals with the T allele for the rs1799722 polymorphism, with a higher calcium intake had significantly higher levels of SBP and diastolic blood pressure (DBP) when compared to CC homozygotes. These findings highlight the interactions between genetic polymorphisms and the consumption of micronutrients on the BP variation.[18]

3.1 Transcriptomics Research Tools in Nutrigenomics

In order to monitor the transcriptome in face of dietary changes, advanced tools are available that open a new future to nutritionists in order to develop tailor-made dietary strategies. These tools are the core of the emerging field of nutrigenomics. Many technologies have been refined to quantify the transcriptome, mainly hybridization-based approaches like microarrays, and sequence-based approaches that directly determine the cDNA sequence such as RNA-seq.

3.2 Microarray

Microarray is a high-throughput technique that allows a fast evaluation of gene expression. It's a quantitative assessment of messenger RNAs (mRNAs) in a cell or

[15] Dariush Farhud & Maryam Shalileh, *Phenylketonuria and its Dietary Therapy in Children*, 18 Iran. J. Pediatr. (2008).

[16] B. H. Leu & J. T. Schmidt, *Arachidonic acid as a retrograde signal controlling growth and dynamics of retinotectal arbors*, 68 Dev. Neurobiol. 18–30 (2008).

[17] *Id.*

[18] Janine Giovanella et al., "Diet-Gene Interaction: Effects of Polymorphisms in the ACE, AGT and BDKRB2 Genes and the Consumption of Sodium, Potassium, Calcium, and Magnesium on Blood Pressure of Normotensive Adult Individuals," *Molecular and Cellular Biochemistry*, November 15, 2020, https://doi.org/10.1007/s11010-020-03983-5.

tissue that is related directly to the level of expression of their corresponding gene.[19] Microarray technology is a powerful tool for the study of gene–diet interactions at the gene expression level. This approach made it possible to study the global impact of diet of a single nutrient on particular human pathology in order to identify the therapeutic properties of a food compound. It also made it possible to have a clear view of the effect of a food compound on the human genes profile in order to understand the mechanism by which different nutrients induce different genes responses.[20] Some applications of the two approaches are provided in the upcoming paragraph.

Hussein et al.[21] demonstrated how high-density microarray experiments have been used to investigate the beneficial effect of astaxanthin (a naturally occurring carotenoid pigment) in kidney glomerular cells of diabetic mice by modifying the expression of some genes that are related to diabetes.[22] Vitamin E compounds have been investigated using microarray techniques to elucidate their role in inhibiting the angiogenesis by downregulating the expression of vascular endothelial growth factor receptor (VEGFR) in endothelial cells.[23]

Albeit its countless advantages, this technique has its fair share of limitations. First, its reliance upon existing knowledge about the genome sequence, meaning that the array can only detect sequences that it was designed to detect. For gene expression analysis, this means that only genes that have already been annotated will be presented on the array.[24] Second, the amount of RNA and its quality is a major challenge for microarray experiments as the quantity and complexity of the obtained sample dictate the quality of RNA that can be isolated, hence why studies are publishing using biological samples that are abundant and easily obtainable.[25] Lastly, microarrays present high background noise levels owing to cross-hybridization which makes it difficult to detect genes with low expression levels.[26] These challenges impose that compromises have to be made, especially in the number and type of samples to be analyzed.

[19] Nicole Dalia Cilia et al., *An Experimental Comparison of Feature-Selection and Classification Methods for Microarray Datasets*, 10 Information 109 (2019).

[20] Aruna Pal, *Nutrigenomics-an emerging area*, 2 Acta Sci. Nutr. Health 12–13 (2018).

[21] Ghazi Hussein et al., *Astaxanthin, a Carotenoid with Potential in Human Health and Nutrition*, 69 J. Nat. Prod. 443–449 (2006).

[22] *Id.*

[23] Kiyotaka Nakagawa et al., *DNA chip analysis of comprehensive food function: Inhibition of angiogenesis and telomerase activity with unsaturated vitamin E, tocotrienol*, 21 BioFactors Oxf. Engl. 5–10 (2004).

[24] Verónica Bolón-Canedo et al., *Challenges and Future Trends for Microarray Analysis*, *in* Microarray Bioinformatics 283–293 (Verónica Bolón-Canedo & Amparo Alonso-Betanzos eds., 2019), https://doi.org/10.1007/978-1-4939-9442-7_14 (last visited Oct 9, 2020).

[25] Giuseppe Russo, Charles Zegar & Antonio Giordano, *Advantages and limitations of microarray technology in human cancer*, 22 Oncogene 6497–6507 (2003).

[26] William J. Brittain et al., *The Surface Science of Microarray Generation–A Critical Inventory*, 11 ACS Appl. Mater. Interfaces 39397–39409 (2019).

3.3 RNA-Seq Technology

Contrasting microarray methods, sequence-based approaches directly determine the cDNA sequences' quality and quantity. At first, Sanger sequencing of cDNA was used but it was relatively low throughput and expensive. Tag-based techniques were developed to overcome these limitations, including Serial Analysis of Gene Expression (SAGE).[27] The study by Mucunguzi et al. used SAGE alongside microarrays to analyze the transcriptome of duodenal mucosa of 7 groups of mice. The authors showed that a total of 896 transcripts were regulated in the duodenal mucosa after "Low Fat" and/or "High Fat" meal, compared to the fasting condition.[28] Cap analysis of gene expression (CAGE)[29] is another technology variant that was used for sequencing total adipose RNA from different groups of healthy non-obese, insulin-sensitive severely obese, and insulin-resistant severely obese human subjects, before and 2 hours into a hyperinsulinemic euglycemic clamp to elucidate that the differences in the acute transcriptional response to insulin are mainly driven by obesity.[30] Massively parallel signature sequencing (MPSS) which has been applied to various living systems including Human[31] and plants,[32] has been used to study the transcriptome of *Arabidopsis thaliana* and demonstrate its complexity.[33] These sequence-based approaches provide precise gene expression levels but only allow a portion of the transcript to be analyzed which limits the annotation of the structure of the transcriptome.

RNA-seq is a recently developed transcriptome profiling technology that uses next-generation deep sequencing platforms. It's a method that allows us to obtain a point-in-time snapshot of the transcriptome.[34] The population of the RNA to be sequenced is converted into a cDNA library, with adapters attached to each end of the fragments, which allows the RNA to be put into an NGS (next-generation

[27] Victor E. Velculescu et al., *Serial Analysis of Gene Expression*, 270 Science 484–487 (1995).

[28] Octave Mucunguzi et al., *Identification of the principal transcriptional regulators for low-fat and high-fat meal responsive genes in small intestine*, 14 Nutr. Metab. 66 (2017).

[29] Rimantas Kodzius et al., *CAGE: Cap analysis of gene expression*, 3 Nat. Methods 211–22 (2006).

[30] Mikael Rydén et al., *The Adipose Transcriptional Response to Insulin Is Determined by Obesity, Not Insulin Sensitivity*, 16 Cell Rep. 2317–2326 (2016).

[31] S. Brenner et al., *Gene expression analysis by massively parallel signature sequencing (MPSS) on microbead arrays*, 18 Nat. Biotechnol. 630–634 (2000).

[32] Blake C. Meyers et al., *Analysis of the transcriptional complexity of Arabidopsis thaliana by massively parallel signature sequencing*, 22 Nat. Biotechnol. 1006–1011 (2004).

[33] *Id.*

[34] William E. Yang, Christopher W. Woods & Ephraim L. Tsalik, *Chapter 13 - Host-Based Diagnostics for Detection and Prognosis of Infectious Diseases*, 42 *in* Methods in Microbiology 465–500 (Andrew Sails & Yi-Wei Tang eds., 2015), http://www.sciencedirect.com/science/article/pii/S0580951715000100 (last visited Oct 6, 2020).

sequencing) workflow.[35] The sequencing of each molecule can be done either unidirectional (single-end sequencing) or bidirectional (paired-end sequencing) and the length of the reads depends on the DNA-sequencing technology which will typically be 30–400 bp.[36] After sequencing, the obtained reads are then aligned to a reference genome database or assembled to obtain de novo transcripts, proving a genome-scale transcriptional map.[37]

Although RNA-seq is a novel technology, it offers several key advantages. First, RNA-seq provides a signal-to-noise advantage because the RNA sequences can be often unambiguously mapped to unique regions of the genome. The noise generated in the experiment can be easily eliminated in the analysis.[38] Second, RNA-seq is not dependent on already known genome data and, therefore, can screen novel transcripts and analyze transcripts structure, unlike microarray technology, which depends on already known genes and genomes.[39] With that said, RNA-seq is a technology that allows high sensitivity and accurate measuring of gene expression across the transcriptome.

High-throughput RNA-seq has become a great approach for discovering and studying transcriptomes or genomes.[40] A study by Peñagaricano et al. used RNA-seq to assess the effect of maternal methionine supplementation on the transcriptome of the preimplantation embryos of Holstein cows. The results demonstrated that the methionine-rich treatment caused 76 genes out of the 276 differentially expressed ones to have higher expression levels than the control group.[41] Another study aimed to demonstrate the influence of the effect of a saturated fatty acid (SFA)- and a monounsaturated fatty acid (MUFA)-rich diet on gene expression profiles of adipose tissue in human subjects at risk of metabolic syndrome showed that the consumption of the saturated fatty acid diet resulted in an increased

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[35] Beena M. Kadakkuzha et al., *Chapter 18 - Genomic and Proteomic Mechanisms and Models in Toxicity and Safety Evaluation of Nutraceuticals*, *in* Nutraceuticals 227–237 (Ramesh C. Gupta ed., 2016), http://www.sciencedirect.com/science/article/pii/B9780128021477000188 (last visited Oct 6, 2020).

[36] Jinglu Wang et al., *RNA sequencing (RNA-Seq) and its application in ovarian cancer*, 152 Gynecol. Oncol. 194–201 (2019).

[37] Kimberly R. Kukurba & Stephen B. Montgomery, *RNA Sequencing and Analysis*, 2015 Cold Spring Harb. Protoc. 951–969 (2015).

[38] Seyed Mehdi Jazayeri, RNA-Seq:Advantages, Disadvantages, Problems, Challenges and Applications (2012).

[39] Beena M. Kadakkuzha et al., *Chapter 18 - Genomic and Proteomic Mechanisms and Models in Toxicity and Safety Evaluation of Nutraceuticals*, *in* Nutraceuticals 227–237 (Ramesh C. Gupta ed., 2016), http://www.sciencedirect.com/science/article/pii/B9780128021477000188 (last visited Oct 6, 2020).

[40] Jay Shendure & Hanlee Ji, *Next-generation DNA sequencing*, 26 Nat. Biotechnol. 1135– 1145 (2008).

[41] Francisco Peñagaricano et al., *Effect of Maternal Methionine Supplementation on the Transcriptome of Bovine Preimplantation Embryos*, 8 PLoS ONE (2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749122/ (last visited Oct 7, 2020).

expression of genes involved in inflammation processes in adipose tissue.[42] A study by Sharma et al., used RNA-seq data to analyze the transcriptome of adipose and liver tissue. It revealed the activation of multiple pathways and genes related to fatty acid-β oxidation (crat, acca2, lonp2, etc.), antioxidative enzymes (gpx1, sod1, nxnl1, etc.), along with the balancing of fatty acid metabolism specifically in black wheat supplemented mice.[43] Another study revealed sex-dependent effect of essential oils (EO) diet in both tissues, and an influence on the expression of genes mainly involved in immune, inflammatory, and stress pathways. Five regulatory genes in liver tissue associated with the EO diet were identified: DNAJB9, MANF, UFM1, CTNNLA1 and NFX1.[44]

4 Nutritional Transcriptomics

Two research approaches are discussed in nutritional transcriptomics, namely a "mechanistic" approach and a "biomarker profiling" approach. The mechanistic approach helps identify nutrient-related molecular and signaling pathways. The biomarker profiling approach's goal is the characterization of early biomarkers that are indicative of a phenotype or a disease state.

4.1 The Mechanistic Approach

Transcriptional profiling is an exceedingly efficient tool in nutrigenomic studies; it helps in identifying and measuring changes in gene expression after a short-term dietary challenge. The ultimate goal of these studies is to identify gene candidates that are responsible for diet-related diseases. This technique allows us to get an overview of almost all cell gene expressions in a single experiment that subsequently reflects the level of gene regulation.[45] Bioactive ingredients in nutrients interact with the DNA, hence the affection of the transcription of RNA and ultimately protein translation (Table 1). The exact mechanism by which nutrients influence gene

[42] Susan J. van Dijk et al., *A saturated fatty acid-rich diet induces an obesity-linked proinflammatory gene expression profile in adipose tissue of subjects at risk of metabolic syndrome*, 90 Am. J. Clin. Nutr. 1656–1664 (2009).

[43] Saloni Sharma et al., "Anthocyanin-Biofortified Colored Wheat Prevents High Fat Diet– Induced Alterations in Mice: Nutrigenomics Studies," *Molecular Nutrition & Food Research* 64, no. 13 (2020): 1900999, https://doi.org/10.1002/mnfr.201900999.

[44] Marcella Sabino et al., "Gene Co-Expression Networks in Liver and Muscle Transcriptome Reveal Sex-Specific Gene Expression in Lambs Fed with a Mix of Essential Oils," *BMC Genomics* 19, no. 1 (April 4, 2018): 236, https://doi.org/10.1186/s12864-018-4632-y.

[45] Aleksandra Adomas et al., *Comparative analysis of transcript abundance in Pinus sylvestris after challenge with a saprotrophic, pathogenic or mutualistic fungus*, 28 Tree Physiol. 885–897 (2008).

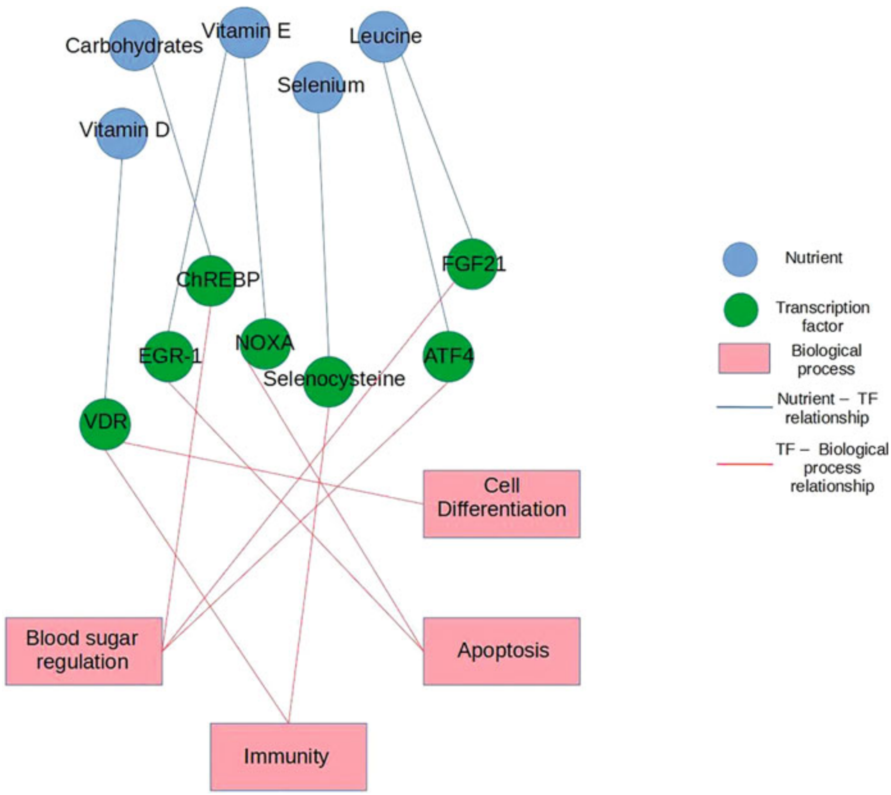

Fig. 1 Nutrients influencing biological processes through transcription factors. The blue circles represent nutrients, the green circles represent transcription factors, and the pink rectangles represent biological processes. The blue lines represent the nutrients–transcription factors relationships, and the pink ones represent the relationship between each transcription factor and the biological process they act in

expression is not fully understood, yet it appears that the transcription factors (TFs) are the main nutrient sensors[46] (Fig. 1). The nuclear hormone receptor superfamily comprises 48 TFs members in the human genome; that is gaining attention as the most important group of nutrient sensors.[47] Many nutrients and their metabolites bind to this superfamily. For example, retinoic acid bind to Retinoic Acid Receptor (RAR) and Retinoid X receptor (RXR),[48] Vitamin D binds to its receptor which does

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[46] Anjana Munshi & V Duvvuri, *Nutrigenomics: Looking to DNA for nutrition advice*, 7 Indian J. Biotechnol. (2008).

[47] D. J. Mangelsdorf et al., *The nuclear receptor superfamily: the second decade*, 83 Cell 835–839 (1995).

[48] G Allenby et al., *Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids.*, 90 Proc. Natl. Acad. Sci. U. S. A. 30–34 (1993).

not only regulate transcriptional responses but is also involved in microRNA-directed posttranscriptional mechanisms,[49] and calorie restriction activate Peroxisome Proliferator-Activated Receptor alpha (PPAR-alpha), also known as NR1C1 (Nuclear Receptor subfamily 1, group C, member 1), which is necessary for the regulation of lipid metabolism in the liver and is activated in the process of ketogenesis.[50]

Nutrients interfere in the signaling pathways. Zaman et al. demonstrated that Sch9 (Protein Kinase Sch9) and PKA (Protein Kinase A) regulate nutrient-responsive transcription in response to different nutrients. For example, when glucose is added to yeast cells an increase in their growth rate was noticed and resulted in a massive restructuring of their transcriptional output. This regulation is done predominantly through the Ras/PKA pathway.[51] Another study highlighted that amino acids (AA) regulate mammalian target of rapamycin complex 1 (mTORC1) activation through the Rag GTPases (hydrolase enzymes that bind to the nucleotide guanosine triphosphate (GTP) and hydrolyze it to guanosine diphosphate (GDP)), which direct the translocation of mTORC1 cytosolic[52] location, to the lysosome via a nutrient-sensitive interaction with Raptor.[53]

4.2 The Biomarker Profiling Approach

Obtaining samples from tissues of interest such as the liver, muscle or adipose tissue, may be a limiting point in human studies because of the invasive nature of biopsies that have to be performed.[54] Hence, why peripheral blood cells (PBCs) are considered to be an alternative is because they can be obtained easily and in sufficient quantities by minimally invasive techniques.[55] PBCs have been proposed as a source of transcriptomic biomarkers of health and disease, because their gene expression

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[49] Thomas S. Lisse et al., *Vitamin D activation of functionally distinct regulatory miRNAs in primary human osteoblasts*, 28 J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 1478–1488 (2013).

[50] Sander Kersten et al., *Peroxisome proliferator–activated receptor α mediates the adaptive response to fasting*, 103 J. Clin. Invest. 1489–1498 (1999).

[51] Shadia Zaman et al., *Glucose regulates transcription in yeast through a network of signaling pathways*, 5 Mol. Syst. Biol. 245 (2009).

[52] *Id.*

[53] Yasemin Sancak et al., *The Rag GTPases Bind Raptor and Mediate Amino Acid Signaling to mTORC1*, 320 Science 1496–1501 (2008).

[54] F.J. Kok, Laura Bouwman & Frank Desiere, Personalized nutrition: Principles and applications (2007).

[55] Paula Oliver et al., *Peripheral blood mononuclear cells: a potential source of homeostatic imbalance markers associated with obesity development*, 465 Pflüg. Arch. - Eur. J. Physiol. 459–468 (2013).

profile reflects in part the expression profile which occurs in other tissues.[56] Changes in gene expression of PBCs might be an indication of the physiological and pathological state of the body that's why transcriptional profiles of these cells are very useful to evaluate the effect of foods and its components.[57] Several studies have shown the association between diet and the transcriptional profiling of PBCs. In a study, changes in the PBC transcriptome have been observed after consumption of diets rich in omega-3 polyunsaturated fatty acids (omega-3 PUFAs) or other dietary modifications.[58] Another study elucidated that the differences in the expression of specific genes in PBCs have been described in children related to the frequency of sugary food or high-fat consumption suggesting that the expression of these genes are potential biomarkers of the frequency of intake of certain nutrients.[59] These examples illustrate how the "biomarker profiling" approach allows the characterization of early biomarkers that are indicative of a phenotype or a disease state.[60]

Nutrigenomics is a revolutionary way of viewing food as an important actor in our overall health. A part of the approaches used in the field involves finding new markers that specify early stages of diet-related diseases; it's at this phase that the intervention with nutrition can recover patients' health. Commonly used biomarkers are often indicative of existing diseases (Table 2), and at this stage, drug treatment is unavoidable. Hence, the necessity to develop a new biomarker concept that is based on the identification of early biomarkers that are indicative of subtle changes in homeostasis.[61] This requires long-term studies with an ultimate goal to identify early biomarkers in the predisease stage to prevent the outcomes by adequate dietary interventions.[62]

[56] Bàrbara Reynés et al., *Specific Features of the Hypothalamic Leptin Signaling Response to Cold Exposure Are Reflected in Peripheral Blood Mononuclear Cells in Rats and Ferrets*, 8 Front. Physiol. (2017), https://www.frontiersin.org/articles/10.3389/fphys.2017.00581/full (last visited Oct 7, 2020).

[57] J. Sánchez et al., *Transcriptome analysis in blood cells from children reveals potential early biomarkers of metabolic alterations*, 41 Int. J. Obes. 1481–1488 (2017).

[58] Vanessa Derenji Ferreira de Mello et al., *Gene expression of peripheral blood mononuclear cells as a tool in dietary intervention studies: What do we know so far?*, 56 Mol. Nutr. Food Res. 1160–1172 (2012).

[59] T. Priego et al., *TAS1R3 and UCN2 Transcript Levels in Blood Cells Are Associated With Sugary and Fatty Food Consumption in Children*, 100 J. Clin. Endocrinol. Metab. 3556– 3564 (2015).

[60] Kok, Bouwman, and Desiere, *supra* note 61.

[61] Ben van Ommen & Rob Stierum, *Nutrigenomics: exploiting systems biology in the nutrition and health arena*, 13 Curr. Opin. Biotechnol. 517–521 (2002).

[62] Kok, Bouwman, and Desiere, *supra* note 61.

Table 2 List of discovered biomarkers and their related pathologies

Biomarker	Related pathology	Publication
Transcription factor NF-kB (nuclear factor kB)	Oxidative stress	Berg et al.[a]
Metallothionein	Heavy metal exposure	Ganguly et al.[b]
Single-minded homologue 2 (SIM2)	Prostate cancer	Arredouani et al.[c]
Vascular endothelial growth factor-A (VEGFA)	β-Type hemoglobinopathy disease severity	Chondrou et al.[d]
Transcriptional modulator H2A histone family, member Y (H2AFY)	Huntington's disease	Mastrokolias et al.[e]
O- linked-N-acetylglucosamine P- (O-GlcNAc) Transferase (OGT)	Maternal stress	Howerton et al.[f]

[a]R. van den Berg et al., *Transcription factor NF-κB as a potential biomarker for oxidative stress*, 86 Br. J. Nutr. S121–S127 (2001).
[b]S. Ganguly et al., *Human metallothionein gene expression determined by quantitative reverse transcription-polymerase chain reaction as a biomarker of cadmium exposure.*, 5 Cancer Epidemiol. Prev. Biomark. 297–301 (1996).
[c]Mohamed S. Arredouani et al., *Identification of the Transcription Factor Single-Minded Homologue 2 as a Potential Biomarker and Immunotherapy Target in Prostate Cancer*, 15 Clin. Cancer Res. 5794–5802 (2009).
[d]Vasiliki Chondrou et al., *Whole transcriptome analysis of human erythropoietic cells during ontogenesis suggests a role of VEGFA gene as modulator of fetal hemoglobin and pharmacogenomic biomarker of treatment response to hydroxyurea in β-type hemoglobinopathy patients*, 11 Hum. Genomics 24 (2017).
[e]Anastasios Mastrokolias et al., *Huntington's disease biomarker progression profile identified by transcriptome sequencing in peripheral blood*, 23 Eur. J. Hum. Genet. 1349– 1356 (2015).
[f]Christopher L. Howerton et al., *O-GlcNAc transferase (OGT) as a placental biomarker of maternal stress and reprogramming of CNS gene transcription in development*, 110 Proc. Natl. Acad. Sci. 5169–5174 (2013).

5 Nutrition System Biology

System biology is an important concept in biological and medical research areas. It is based on the reality that organisms exist as a system and the better we understand the interactions between them, the sooner we can develop effective preventive or treatment strategies addressing health issues (Fig. 1).[63] Nutrigenomics is an important part of systems biology, from its research concept to its practical application. Nutrigenomics deals with the interactions between nutrients and genes. It reflects the interaction between an environmental factor (nutrients) and our biological systems (genes and gene products). Before we can evaluate the nutrient–gene interactions, the bioavailability and tissue concentration of nutrients, including digestion, absorption, transportation, distribution and the individual variations. The assessment of

[63] Jing X. Kang, *Nutrigenomics and systems biology*, 5 J. Nutr. Nutr. I–II (2012).

nutrigenomic effects requires a thorough inspection of at least three interconnected systems, nutrient–nutrient, nutrient–gene and gene–gene interactions.[64]

With the emergence of various technology revolutions, the building blocks for a systems physiology approach were set. Metabolomics technologies have been used to elucidate that the metabolic response is dependent on the quantity and timing of exposure to bioactive food components. Its applications to studies for dietary interventions allow a greater understanding of the effect of an individual's diet on undergoing metabolic changes.[65] The integration of numerous human nutrigenomics studies with multiple omics knowledge bases empowers the creation of combined theoretical and observation networks that provide a systems view of particular types of nutritional interventions to promote health and well-being.[66]

Systems biology is an emerging approach having a massive potential in the advance of the probiotic and prebiotic development field.[67] It creates a new era of designed probiotics/prebiotic that have therapeutic applications to enhance the immune and metabolism system.[68] They have been administered to confer a health benefit on the host in various diseases such as diabetes[69] and hypertension.[70]

In a recent study, a system biology approach helped identify an oxidative stress biomarker, plasma disulfide Cysteine/Glutathione (CySS/GSH) R-ratio, that predicted death in coronary artery disease human patients and renewed interest in oxidative stress as an important disease mechanism. It also highlighted the important nature of a holistic redox systems approach for studying nutrition and oxidative stress due to the broad array of causes of oxidative stress that is balanced by an equally broad range of antioxidant systems.[71] Recent integrated system biology research and omics advances made it feasible for redox network analysis to be studied in which dietary factors are systematically varied and oxidative stress markers are linked through the use of computational methods. Hence, redox systems

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[64] Venter et al., *supra* note 2.

[65] Marie-Laure Bayle et al., *Semi-targeted metabolomic approaches to validate potential markers of health for micronutrients: analytical perspectives*, 8 Metabolomics 1114–1129 (2012).

[66] Thomas Kelder et al., *White adipose tissue reference network: a knowledge resource for exploring health-relevant relations*, 10 Genes Nutr. (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252261/ (last visited Oct 6, 2020).

[67] Monika Yadav and Pratyoosh Shukla, "Recent Systems Biology Approaches for Probiotics Use in Health Aspects: A Review," *3 Biotech* 9, no. 12 (November 11, 2019): 448, https://doi.org/10.1007/s13205-019-1980-5.

[68] Monika Yadav & Pratyoosh Shukla, *Recent systems biology approaches for probiotics use in health aspects: a review*, 9 3 Biotech 448 (2019).

[69] Shih-Hung Wei, Yen-Po Chen & Ming-Ju Chen, *Selecting probiotics with the abilities of enhancing GLP-1 to mitigate the progression of type 1 diabetes in vitro and in vivo*, 18 J. Funct. Foods 473–486 (2015).

[70] J. E. Aguilar-Toalá et al., *Postbiotics: An evolving term within the functional foods field*, 75 Trends Food Sci. Technol. 105–114 (2018).

[71] Kristine K. Dennis, Young-Mi Go & Dean P. Jones, *Redox Systems Biology of Nutrition and Oxidative Stress*, 149 J. Nutr. 553–565 (2019).

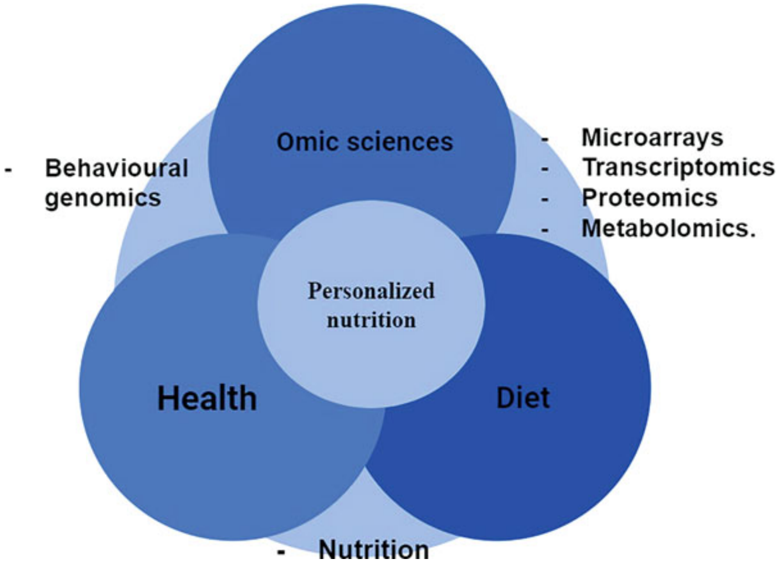

Fig. 2 A schematic representation of the integration of the "Omics" sciences, diet, and health toward personalized nutrition

nutrition is assured to support the development of advanced methods to use diet and nutrition to protect against oxidative stress and disease.[72]

With the principles of systems biology in mind, we ought to perceive the complexity of biological systems and use an integrated approach to investigate the interactions between nutrients and genes at all potential omics levels. Thus, we will be able to obtain reliable and comprehensive information for the development of personalized nutrition (Fig. 2).

5.1 Challenges in Nutrigenomics

The "omics-based" analytical strategies and next-generation sequencing methods cannot be ignored because of their great potential in nutrigenomics studies. The associated cost of these initiatives is decreasing, while the efficiency and pace of detection are increasing. These new tools allow the availability of more elaborative transcriptomics, proteomics, and metabolomics data for even more advanced studies. Despite the considerable focus on nutrigenomics research, little has been developed toward health consequences and personalized medicine. The concept of personalized nutrition still awaits enough support, concerted efforts, and comprehensive

[72] Kristine K. Dennis, Young-Mi Go & Dean P. Jones, *Redox Systems Biology of Nutrition and Oxidative Stress*, 149 J. Nutr. 553–565 (2019).

molecular information about the onset of diseases, the genetic makeup of people, and food variability.[73] Variability within the amount and kinds of dietary constituents and bioactive compounds in several foods, the composition of diets, and methods of food preparation have emerged as bottlenecks in generalizing the principles of molecular nutrition and personalized diets for a specific population. Other issues are associated with the differences in targets of bioactive compounds, affinity toward target sites, and internutrient interactions within the body tissues. Moreover, the interactions between ongoing medications and dietary nutrients don't seem to be fully understood.

Being a multifaceted emerging field of science, nutrigenomics presents ethical issues concerning the extent to which it's going to improve individual and public health within society. These ethical aspects should be considered thoroughly while applying them for designing personalized nutrition strategies.[74] A powerful need is felt to line ethical and scientific guidelines for nutrigenomics research for the gathering, analysis, interpretation, implementation, and archiving of nutritional and omics data.[75] Several ethical issues like stress in individuals for possible disease development and the privacy of people may well be compromised. Nutrigenetics data could be employed by insurance companies to deny insurance to individuals for a particular disease that needs immediate attention.[76] Deciphering the gene–diet interaction won't only function as a guide to human consumption behavior but also to boost the longevity of the human species by preventing diet-related diseases and disorders.

6 Conclusion

The science of precision nutrition has made great progress, but gene–diet interactions are becoming more complex due to the novel food product developments. The "omics" will surely provide a better understanding of factors that influence the

[73] Pritesh Vyas et al., "Nutrigenomics: Advances, Opportunities and Challenges in Understanding the Nutrient-Gene Interactions," *Current Nutrition & Food Science* 14, no. 2 (2018): 104–15, https://doi.org/10.2174/1573401313666170614094410.

[74] Cristiana Pavlidis, George P. Patrinos, and Theodora Katsila, "Nutrigenomics: A Controversy," *Applied & Translational Genomics* 4 (February 14, 2015): 50–53, https://doi.org/10.1016/j.atg.2015.02.003.

[75] Nicola Luigi Bragazzi, "Situating Nutri-Ethics at the Junction of Nutrigenomics and Nutriproteomics in Postgenomics Medicine," *Current Pharmacogenomics and Personalized Medicine* 11, no. 2 (June 2013): 162–66, https://doi.org/10.2174/1875692111311020008.

[76] Allal Ouhtit, "Nutrigenomics: From Promise to Practice," *Sultan Qaboos University Medical Journal* 14, no. 1 (February 2014): e1-3, https://doi.org/10.12816/0003328.

phenotype and its relationship to health.[77] A personalized nutritional strategy approach will be required in the future because it will allow the prevention measures to block or suppress the initiation, promotion and progression of pathways that lead to an unhealthy or lethal phenotype.[78] Although the promotion of health and prevention of disease are long-standing goals of nutrition science, the powerful tools of molecular biology and computational power of bioinformatics are accelerating progress toward these goals. This will raise challenging questions and issues as the number of data will accumulate. As always, it will be upon scientists and physicians to analyze the data and deliver sound science and medical advice. Multiomics approaches need to be implemented to obtain a better understanding of food microbial ecosystems. However, few examples are available in literature which might be due to certain limitations of this type of approaches, like the relatively high cost and the need for specific bioinformatics and biostatistics skills for the data analysis. Finally, the success of these nutritional approaches will depend on the ability to identify and validate nutrigenetic, nutritional epigenetic, proteomic, and metabolomic biomarkers to determine cause, effect and susceptibility to disease. It also depends on the ability of healthcare consumers to understand the value of genomic information in developing a personalized nutrition plan.

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[77] Dolores Corella, "Nutrigenética, Nutrigenómica y Dieta Mediterránea: Una Nueva Visión Para La Gastronomía," *Nutrición Hospitalaria* 35, no. 4 (June 12, 2018), https://doi.org/10.20960/nh.2120.

[78] Deepika Laddu and Michelle Hauser, "Addressing the Nutritional Phenotype Through Personalized Nutrition for Chronic Disease Prevention and Management," *Progress in Cardiovascular Diseases*, Merging Precision and Healthy Living Medicine: Tailored Approaches for Chronic Disease Prevention and Treatment, 62, no. 1 (January 1, 2019): 9–14, https://doi.org/10.1016/j.pcad.2018.12.004.

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Modeling of Food and Nutrition Security: Relevance of the PLS Approach to Structural Equation Models

Mohamed Ech-Chebany, Anas Hattabou, Adil Ouatat, Aomar Ibourk, and Faycal Goujgal

Abstract Structural equation models with latent variables are originally developed by Jöreskog (A general method for estimating a linear structural equation system. u Structural equation models in the social sciences, urednici AS Goldberger i OD Duncan, 85–112, in: Njujork, SAD: Seminar: 1973), Keesling (Maximum likelihood approaches to causal analysis: 1972) and Wiley (Identification problem for structural equation models with unmeasured variables. United States of America: 1973) to examine multiple causal relationships. The two most widely answered procedures in the literature on structural equations are the **Li**near **S**tructural **Rel**ationships (LISREL) method and the **P**artial **L**east **S**quare (PLS) method. The PLS method, proposed by Wold (Syst Indirect Obs 2:343: 1982), is based on the use of Partial Least Squares regression techniques for estimating models of structural equations. Indeed, structural equation models are the most suitable for modeling food phenomena approached from the perspective of the capability approach. These socioeconomic phenomena are usually represented by capability areas (capability), with each of them resulting in at least one operation (indicator). Thus, a capability is a combination of a set of operations that is not directly measurable by its functions. Likewise, the dimensions of "Food and Nutritional Security (FNS)" are not directly observable, but each can be understood by a set of indicators. After having exposed the principle of each of the two methods LISREL and PLS, we will concern ourselves in this article to demonstrate how the PLS method would be a relevant method for understanding "FNS" through its four dimensions which are "availability", "accessibility", "stability" and "use".

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Keywords Food and Nutritional Security (FNS) · Capability approach · Structural equation models · PLS method

1 Introduction

Structural equation models with latent variables are originally developed by Jöreskog (1973), Keesling (1972) and Wiley (1973) to examine multiple causal relationships. Their use has been extended to analyses of construct validity (analysis confirmatory factorial) and then to multigroup analyses and longitudinal studies (Lacroux 2009). The main interest of these relational models lies in their ability to simultaneously estimate dependency relationships between several independent latent variables and several latent dependent variables.

There are several procedures for estimating structural equation models which differ from each other by the type of algorithm to which they are used. However, the two most widely answered procedures in the literature on structural equations are the **Li**near **S**tructural **Rel**ationships (LISREL) method and the **P**artial **L**east **S**quare (PLS) method.

The LISREL estimation method, born from the work of Karl Jöreskog in the early seventies, is based on the analysis of covariances (Covariance-Based Structural Equation Modeling, CBSEM) and generally uses the maximum likelihood estimator. On the other hand, the PLS method, proposed by Wold (1982), is based on the use of Partial Least Squares regression techniques for estimating models of structural equations. The principle of this method is based on the analysis of variance (*Variance-Based Structural Equation Modeling* (VBSEM)) and on the optimization of the explanatory power of the indicators.

Indeed, structural equation models are the most suitable for modeling food phenomena approached from the perspective of the capability approach. These socioeconomic phenomena are usually represented by capability areas (capability), with each of them resulting in at least one operation (indicator). Thus, a capability is a combination of a set of operations that is not directly measurable by its functions. Likewise, the dimensions of "food and nutritional security (FNS)" are not directly observable, but each can be understood by a set of indicators. Formally, each of these dimensions (capabilities) is a latent variable in the structural equation modeling, and each latent variable (dimension where capability) is measured by a set of manifest variables (operations). All the operations with their capability (size) represent the measurement model, and all the relationships between the four dimensions of the "Food and Nutrition Security (FNS)" represent the structural model.

After having exposed the principle of each of the two methods LISREL and PLS, we will concern ourselves in this article to demonstrate how the PLS method would be a relevant method for understanding "Food and Nutritional Security (FNS)" through its four dimensions which are "availability", "accessibility", "stability" and "use".

2 Methods of Estimating Structural Equation Models with Latent Variables

2.1 Methods of Structural Equations with Latent Variables

Structural equation models with latent variables are originally developed by Jöreskog (1973), Keesling (1972) and Wiley (1973) to examine multiple causal relationships. Their use has been extended to analyses of construct validity (analysis confirmatory factorial) and then to multigroup analyses and longitudinal studies (Lacroux 2009). The main interest of these relational models lies in their ability to simultaneously estimate dependency relationships between several independent latent variables (also called explanatory or exogenous) and several dependent latent variables (also said to be explained or endogenous). In structural equation modeling, a latent variable is a variable which is not directly observable and therefore cannot be directly measured. On the other hand, a manifest variable could collect a direct measurement. The latent variables are then estimated from the manifest variables by dissociating their share from the common variance (e.g., in Fig. 1, the latent variable η_1 is measured by the manifest variables X_{11}, X_{12} andX_{13}). The models of structural equations correspond to a system of equations represented as a directed graph where the nodes represent the manifest variables (X_{11}, X_{12}, X_{13}, . . .) as a square and the latent variables (η_1, η_2 and $_1$) as a circle, and the causal links between variables (β_1, β_2 and β_3)are represented by arrows or arcs (see Fig. 1). In these models, each

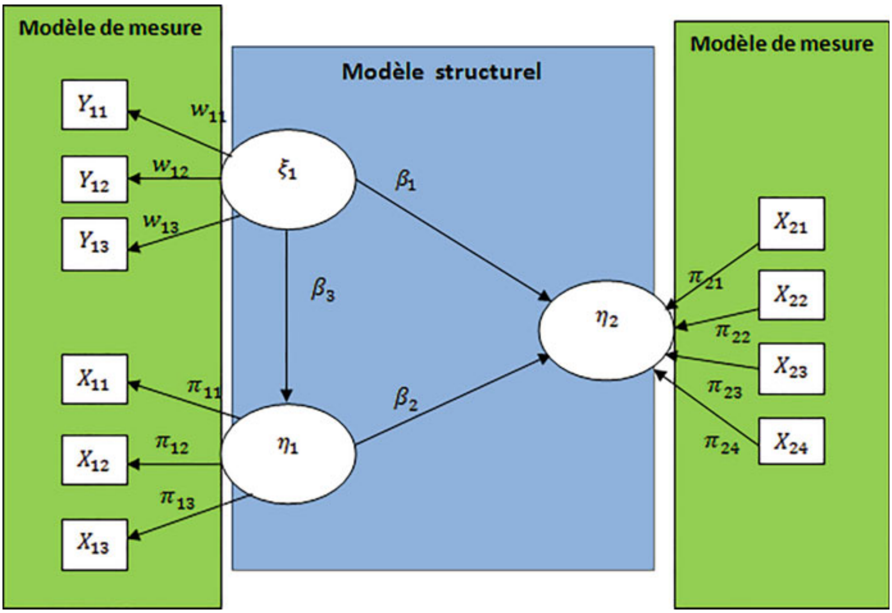

Fig. 1 Diagram of a structural equation model

manifest variable is associated with a single latent variable; on the other hand, the latent variables can be related to each other.

A structural equation model is made up of two types of models: the measurement model (or external model) and the structural model (or internal model) (see Fig. 1). The measurement model traces all the relationships that exist between each latent variable and its manifest variables. Thus, the measurement model allows the identification and estimation of latent variables from their manifest variables. On the other hand, the structural model represents all the causal relationships between the latent variables (also known as latent constructs), and it thus makes it possible to trace the meaning of the hypotheses constituting the research model to be tested.

The processing of structural equation models is based on four standardized steps (Lacroux 2009):

- The specification of the model: It aims to develop a conceptual model representing the research hypotheses in the form of a relational diagram.
- Model identification: This step makes it possible to ensure whether it is theoretically possible to obtain an estimate for all the parameters making up the model.
- Operationalization of measurement scales, collection and preparation of data to be analyzed.
- The estimation of the model: It makes it possible to obtain the value of the parameters and to examine the quality of fit of the model to the empirical data.

2.2 *Specification of Structural Equation Models: Reflective Constructs Versus Formative Constructs*

During the specification phase, researchers develop their conceptual models that summarize all of their research hypotheses. At this stage, it is undeniable to distinguish between reflexive constructs and formative constructs; any error in the specification of the nature of the construct has directly harmful consequences on the conclusions drawn from the research (Fernandes 2012).

Classical test theory dominated by the Churchill paradigm (Churchill Jr 1979) advocates a reflective construct. In this type of construct, all indicators are assumed to represent the influence of their construct, and hence each manifest variable reflects its latent variable. It follows that all the indicators agree in their way of measuring the phenomenon represented by the construct, and therefore, all reflect this same construct. Then, the direction of the links of causality operates from the construct to its indicators (e.g., in Fig. 2, ξ_1 is a reflexive construct, the arrows (directions of causality) go from the construct ξ_1 to its indicatorsY_{11}, Y_{12} and Y_{13}). The reflexive construct is then considered as the common cause shared by all its indicators, formally, and each manifest variable is linked to its latent variable by a linear regression model (e.g., in Fig. 2, $Y_{11} = \pi_{11}\xi_1 + \epsilon_{11}$, π_{11} represents the loading linking the manifest variable Y_i to the latent variable ξ_1). From the above, all the indicators (manifest variables) must be significantly and positively correlated, and

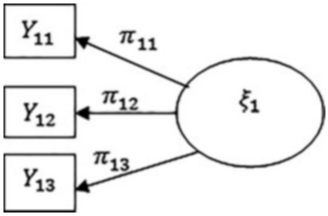

Fig. 2 Reflective construct

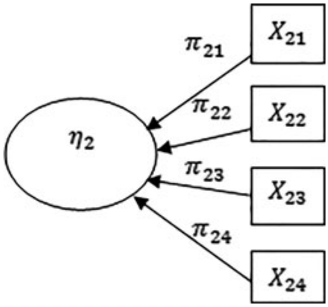

Fig. 3 Formative construct

therefore, any variation in the construct must be accompanied as faithfully as possible by the variation of all the items of the same construct (Lacroux 2009). It emerges that in the presence of a reflexive construct, the researcher will be led before the estimation of his model of structural equations to begin his treatment with the phase of purification (or purification) of the items to ensure the unidimensionality of the construct, its validity, its internal consistency and the positive sign of the correlations of the indicators with their latent variable. Finally, at the practical level, reflective constructs are more suited to attitudinal variables (e.g., involvement, feeling of justice, well-being, etc.).

However, it is possible to end up with models containing one or more formative constructs (Blalock 1971; Bollen and Ting 2000). A formative construct is a linear combination of indicators (also called indexes), not necessarily correlated, which measure theoretically different phenomena, and which contribute to forming the latent variable. In this case, and conversely to the reflexive construct, the direction of causality goes from the indicators toward their latent construct (e.g., in Fig. 3, η_2 is a formative construct, the arrows (directions of causality) go from the indicators (X_{21}, X_{22} andX_{23}) toward the constructη_2). Formally, the latent variable is represented by a linear function of the manifest variables plus a random term (e.g., in Fig. 3, $\eta_2 = \pi_{21}X_{21} + \pi_{22}X_{22} + \pi_{23}X_{23} + \epsilon_{11}$ with π_{ij} the weight binder manifest variable X_{ij} to the latent variable η_2). As a result, a formative construct, unlike a reflective construct, can be multidimensional and thus represents a group of indicators which do not necessarily share a common theme, but which must simultaneously frame the conceptual and empirical meaning of the construct in question. It follows that a positive correlation between the manifest variables is possible, but it is not a necessary condition as in the case of the reflexive construct. On a practical level, the example of the formative construct, commonly put forward by researchers, is the scale for measuring the socioeconomic status of an individual, which is composed of a combination of four indicators (not necessarily correlated) which are level of education, annual income, job held and place of residence (Hauser 1972).

In addition to reflective and formative constructs, there is a third type of latent variable called mixed. We then speak of MIMIC mode (Multiple Indicators Multiple Causes) when a construct is made up of both reflective and formative indicators. This type of latent variable (Hauser and Goldberger 1971; Jöreskog and Goldberger 1975) can be interpreted in three different ways: as a single construct with two types of manifest variables, as a combination of exogenous variables influencing a single reflexive construct, and finally as a composite construct which influences two different reflexive constructs. However, these different configurations are empirically indistinguishable because they lead to the same estimates.

The distinction between reflexive and formative constructs is of crucial importance when modeling in structural equations. Indeed, a poor specification of the nature of the construct inevitably influences the quality of the measurement model, which impacts the validity of the results at the level of the structural model (Anderson and Gerbing 1988; Jarvis et al. 2003; MacKenzie et al. 2005).

Consequently, the statistical treatment will be different at the level of the evaluation of the validity and the consistency of the measurement scales according to the nature of the reflective or formative construct. Thus, the classical procedures massively used for the validation of measurement scales are based on the hypothesis of the positive correlation between the indicators, and therefore, they are appropriate for the evaluation of reflective constructs. It mainly concerns procedures for verifying the unidimensionality of constructs and for cleaning up measurement scales. These methods automatically lead to rejecting indicators having a weak correlation with the others. For this reason, these approaches remain inappropriate in the case of a formative construct, since they can lead to the elimination of items that may be relevant in the research. In fact, first of all, a formative construct is measured by a set of indexes (also called statements or elements) representing the different dimensions which do not necessarily share a common theme, and therefore, it is by nature a multidimensional construct. In addition, the indexes of a formative construct may or may not be correlated and may even have a negative correlation, which implies that the procedures of internal consistency have no meaning. Finally, there is no rigorous methodology that is unanimous among researchers for the validation of this kind of construct (Lebrument 2012). To remedy these shortcomings, Diamantopoulos and Siguaw (2006) have proposed procedures which allow the selection of a large number of indexes in order to minimize the variance of the latent variable not explained by its items. Their approach is based on massive recourse to the literature relating to the concept studied to validate a formative construct, since the abusive elimination of indexes relating to a concept can impoverish the meaning and the predictive power of this type of construct.

Finally, the bad specification at the level of the latent constructs can lead to questioning the quality of the results obtained on the structural models and therefore lead to false conclusions on the research hypotheses (structural relations). According to Jarvis et al. (2003) and MacKenzie et al. (2005), specification errors at the level of latent constructs can lead the researcher, for example, to overestimate structural coefficients and therefore to favor relationships when they are not significant.

2.3 Methods of Estimating Structural Equation Models: LISREL Versus PLS

2.3.1 LISREL Method

The methods for estimating structural equation models make it possible to calculate the numerical value of the links between the indicators and their latent constructs in the case of the measurement model, and to calculate the structural coefficients (numerical values of the links between the latent constructs of the model) for the case of the structural model. There are several procedures for estimating models of structural equations which differ from each other by the type of algorithm to which they use. Among these are:

- the LISREL method (***Li****near* ***S****tructural* ***Rel****ationships*): This method makes use of analysis of covariance structure and uses the approach of maximum likelihood; it assumes the multinormality of the data;
- GLS method (***G****eneralized* ***L****east* ***S****quares)*: This method is less sensitive to the nonnormality of the data but on the other hand remains very sensitive to the complexity of the model;
- the ADF methods (***A****symptotic* ***D****istribution* ***F****ree*) and WLS (***W****eighted* ***L****east* ***S****quares*): These two methods do not involve the multinormality data but by against require a higher sample size (more than 2500 individuals statistics);
- PLS method (***P****artial* ***L****east* ***S****quare*): It is based on the analysis of the variance and is based on the approach of lesser s square partial.

We will limit ourselves in what follows to the two procedures the most answered in the literature on structural equations, which are the LISREL method and the PLS method.

The LISREL estimation method, born from the work of Karl Jöreskogin in the early 1970s, is based on the analysis of covariances (Covariance-Based Structural Equation Modeling, CBSEM) and generally uses the maximum likelihood estimator. This method is known in the literature under several names, the main ones being LISREL, structural equation modeling (SEM), covariance structure analysis, etc. In this work, and for the sake of simplicity, we will use the term LISREL. From the theoretical model built by the researcher following a review of the literature, the LISREL method makes it possible to constitute a theoretical covariance matrix made up of the expected correlation coefficients. From the observed data, the data actually collected, another covariance matrix, called the observed or empirical covariance matrix, will be constructed and composed of the correlation coefficients between the variables taken in pairs. Thus, the principle of the LISREL method is based on estimating the parameters of the model iteratively, so as to minimize the difference between the two theoretical and empirical matrices.

Let $\sum$ be the theoretical covariance matrix; S the empirical covariance matrix; η_1, η_2 andξ_1 the latent variables shown in the model of Fig. 1.

$$\eta_2 = \beta_1\xi_1 + \beta_2\eta_1 + \epsilon_2 \tag{1}$$

$$\eta_1 = \beta_3\xi_1 + \epsilon_1 \tag{2}$$

With β corresponding to the regression coefficient and ϵ the error term.

The theoretical covariance matrix corresponding to the model described by the two equations (Eq. 1 and Eq. 2) will then be:

$$\Sigma = \begin{pmatrix} var\xi_1 & & \\ cov(\eta_1\xi_1) & var\eta_1 & \\ co(\eta_2\xi_1) & cov(\eta_2\eta_1) & var\eta_2 \end{pmatrix} = \begin{pmatrix} \sigma_1^2 & & \\ \sigma_{12} & \sigma_2^2 & \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 \end{pmatrix}$$

Similarly, we express the covariance between η_2 and η_1 as follows:

$$co(\ \eta_2\eta_1) = \sigma_{23} = cov(\beta_1\xi_1 + \beta_2\eta_1 + \epsilon_2, \eta_1) = \beta_1\sigma_{12} + \beta_2\sigma^2$$

Therefore, it would be simple to express the theoretical covariance matrix by several equations containing the following parameters: the regression coefficients β, the variances of the independent variables σ^2, the covariances between independent variables σ and finally the variance of the errors that will be noted. All these parameters will be represented by a vector denoted by Θ. For the model of structural equations shown in Fig. 1, this vector can be written as:

$$\Theta = (\beta_1, \beta_2, \beta_3, \sigma_{12}, \psi_1, q_2)$$

Thus, the LISREL procedure consists in estimating Θ while minimizing the residuals between the two matrices$\sum$ (theoretical) and S (empirical), in other words, in making the theoretical matrix as close as possible to the empirical matrix by using the approach maximum likelihood (maximum likelihood (ML)). The likelihood function that must be maximized in our case can be formulated as follows:

$$F_M(\Theta) = \log\ \left|\sum(\ \Theta)\right| + tr\ \{S\sum(\ \Theta) - 1\} - log|S| -$$

With tr being the trace of the matrix and q the number of observed variables.

In summary, the idea underlying the principle of modeling by the LISREL method is the reconciliation between the theoretical matrix of covariances, resulting from a theoretical (conceptual) model pre-established by the researcher, and the empirical matrix formed from the actual data collected in the field of the study. In view, the LISREL method is mainly used to confirm a theory, and it is then a confirmatory method which requires a solid theoretical construction to develop the research model to be tested. Likewise, recourse to the maximization of the likelihood function inevitably implies that the researcher must respect the conditions of multinormality of all the indicators (items) used and that the latter must be continuous or interval. It emerges that the application of this method is mainly conditioned by the multinormality of the data, the linearity of the model, the independence of the observations, the unidimensionality of the latent constructs and finally by a number of relatively large observations (minimum 200 observations according to Roussel et al. (2002)). Likewise, according to several studies, the two most difficult conditions to meet are, in general, the normality of the data and the number of observations (sample size). However, the violation of the condition of the normality of the data leads to bias the estimates of the parameters (especially with small samples (100 observations)), to have a direct effect on the estimate of the loadings and the structural coefficients, to make sensitive the importance of the sample size and ultimately to have an effect on the Chi-square test which is one of the parameters of the goodness of fit of the model (Lei and Lomax 2005).

2.3.2 PLS (*Partial Least Squares*) Method

The PLS method, proposed by Wold (1982), is based on the use of Partial Least Squares regression techniques for estimating models of structural equations. The principle of this method is based on analysis of variance (*Variance-Based Structural Equation Modeling* (VBSEM)) and on the optimization of the explanatory power of the indicators. Thus, the estimation of the parameters will be carried out iteratively: First of all, the latent variables will be estimated in the framework of the measurement model by linear combinations of their weighted indicators, and then the links between the latent constructs will be estimated by multiple regressions between these same constructs, up to the point where the variance explained by the dependent variables by the independent variables is maximum.

By analogy with factor analysis, the difference between the LISREL method and the PLS method is of the same order as that between classical factor analysis and principal component analysis (Lacroux 2009). Indeed, principal component analysis always allows a solution without taking into account measurement errors. Thus, the PLS approach makes it possible to avoid all inadmissible solutions and indeterminate factors and obtain an admissible solution. It is used in a purely predictive approach where the main objective is to obtain a prediction of the independent variables as a function of the dependent variables.

Unlike the LISREL method, the PLS method does not require multinormality of variables and adapts to continuous, metric and nominal variables. Likewise, it can be used for reflective and formative constructs. It requires fewer observations, as opposed to the LISREL method which requires at least a sample of 200 (Roussel et al. 2002), and the PLS method works with reduced samples even with a complex structural model. Thus, the minimum number of observations required for estimation with the PLS method must be equal, according to the rule of Chin (1998), to 10 times the number of relations emanating from the central construct of the model, that is to say, we multiply by 10 the number of latent construct bound manifest variables which is linked with the most manifest variables. This characteristic is very important in the social sciences where it is generally difficult to work with samples that are too large.

On the other hand, by difference to the LISREL method which adapts well to confirmatory analyses which suppose the use of a very solid and well-founded theoretical construction, the PLS method is very suitable for estimating models not yet established by theory. In this sense, Jöreskog and Wold (1982) predict that "the maximum likelihood method is theory-oriented and emphasizes the transition between exploratory and confirmatory analysis. PLS's primary objective is causal and predictive analysis within the framework of complex models but developed on a limited theoretical basis".

Finally, the PLS method appears to be well suited to testing partial models and to exploratory analyses in which it is difficult to constitute a large sample and to have widely tested measurement scales (Hair et al. 2017, 2019; Sosik et al. 2009).

However, and despite all its advantages, the PLS approach has a number of limitations. Indeed, not taking into account measurement errors constitutes the most important limitation of this approach, which reduces the quality of the estimation of the model, this consequently leads to an underestimation of the structural model (structural coefficients) and to an overestimation of the measurement model (factorial contributions (loadings)). To overcome this problem, McDonald (1996) proposes to have a number of very important items per latent variable and work on very large samples.

Likewise, unlike the LISREL method, the PLS method does not allow so-called nonrecursive models to be tested because of its algorithm based on multiple regression techniques. Thus, only models comprising unambiguous structural relations are testable with the PLS approach (Jöreskog and Wold 1982).

Finally, one other limit inherent in the PLS approach is that relating to the absence of fit indices. Indeed, and unlike the LISREL method, users of the PLS method do not have adjustment indices that allow the model tested to be adjusted to empirical data (Bennaceur and Chafik 2019). However, this does not mean that the models estimated by the PLS algorithm cannot be evaluated, there is a panoply of calculations (factorial contributions, coefficient of determination and certain procedures (bootstrap and jackknife)) to ensure the significance of the estimated coefficients (Lacroux 2009).

3 Relevance of the PLS Approach in the Modeling of "Food Security and Nutrition (FSN)": Capability Approach

3.1 "Food Security and Nutrition (FSN)" Seen from the Perspective of the Capability Approach: Theoretical Framework

Standard economic analysis of food and nutrition security issues is generally viewed from the perspective of three approaches. The Malthusian approach to food availability, the income approach and the sustainable livelihoods approach. These approaches, often referred to as classic approaches, have repeatedly shown their limits in gaining an in-depth understanding of recent food issues, especially related to nutrition (Lankouande and Sirpe 2020). In this context, two emerging economic approaches are currently the most used to study phenomena relating to food and nutrition security (Burchi and De Muro 2016): the rights approach and the capabilities approach (CA) of Sen (1981).

According to Sen (1981), hunger is the direct cause of failure to have the right to have enough food at all times. Thus, and beyond food availability, two other aspects must be considered: accessibility to food and the stability of supplies. This approach was widely disseminated within the community of economists under the name of the rights approach (Sen 1981) during the 1980s. However, several studies have shown the inadequacy of this approach in explaining issues relating to food security and nutrition (Burchi and De Muro 2012; Lankouande and Sirpe 2020; Sen 1985). Indeed, the main criticism intended for the rights-based approach is the fact that it uses the concepts of food security and nutrition separately at a time when several studies have shown that these two concepts are linked (Lankouande and Sirpe 2020).

In 1985, Sen proposed a new approach called the capability approach. In this new conceptual framework, Sen distinguishes two different concepts: the means available and the use of these means. Thus, the capability approach allowed the theoretical reconciliation between the two concepts of food security and nutrition which gave birth to the concept of food security and nutrition (FSN).

The capability approach is made up of the interdependence of two concepts: operation and capability. The operation references to what an individual can aspire to be or do (food, clothing, be healthy), while the capability expresses all operations that is to say all real possibilities held by an individual to be and do (eat decently, live a life worth living). Therefore, the capability approach provides an analytical framework for understanding the way in which people develop their "capacity to be freed from hunger" (Lankouande and Sirpe 2020). Thus, this approach distinguishes between the means available or to be mobilized and the purpose of these means. In this sense, Sen emphasized that the relationship between food intake (average) and feed efficiency (aim) depends on several personal and social criteria (age, gender, income, etc.), level education and health conditions, etc.

The major contribution of the capability approach is the integration of the "use" dimension in the definition of Food Security and Nutritional (FSN). This integration has helped make the connection between the concept of "food security" and the concept of "nutrition" in a single conceptual framework is the "Food Security and Nutrition (FSN)" in which the two concepts have been treated until now separately. From then on, the capability approach has enriched the concept of "Food Security and Nutrition (FSN)" by focusing on the "purpose" and goes beyond the "food intake". This gave rise to the need to move from food rights to nutritional capacities in the analysis of questions relating to the problems of hunger.

Burchi and De Muro (2012, 2016) have proposed an analysis of "Food and Nutrition Security" through the capability approach. For these authors, the capability analysis of FSN necessarily goes through three phases: food rights, basic FSN capacities, and the capacity to provide FSN. The phase of food rights emphasizes on what populations have and what they do and therefore addresses three distinct dimensions: the "availability" dimension which represents the endowments available to the individual, the "accessibility" dimension which reflects the individual's ability to access exchange or production, and finally the "stability" dimension which makes it possible to analyze whether the individual has enough food to live adequately today and in the near future (variations in endowments and exchange conditions). The second phase refers to the institutional (rules, uses, etc.), environmental (climatic hazards) and other basic capabilities (health, education and social justice) factors that can influence the ability to be released of hunger. The third phase emphasizes on the "use" dimension and therefore goes beyond analyses in terms of basic capacities and their interactions to apprehend qualitative aspects such as information on nutritional status, quality and variety of food, nutritional practices and knowledge. Thus, with the "use" dimension, the capability approach has made it possible to enrich the field of food's analysis issues by emphasizing on the nutritional capacities necessary for human well-being, unlike traditional approaches which focus on insufficient food and mechanical monitoring of nutritional requirements.

3.2 Modeling of "Food and Nutritional Security": Relevance of the PLS Structural Equations Method

Empirically, the studies focus on the analysis of relationships that may exist between the four dimensions of "Food and Nutrition Security" that are "availability", "accessibility", "stability" and "the use". Some of these studies have shown that these dimensions are interrelated.

In this sense, Lankouande and Sirpe (2020) conducted a synthesis of empirical studies analyzing the relationship between the four dimensions of the "Food Security and Nutrition (FSN)". According to this synthesis, Azoulay and Dillon (1993) studied the relationship between food availability which is the "availability dimension" and meeting the nutritional needs representing the "use dimension". They found that the availability of food (availability dimension) could be a necessary condition, but not sufficient for meeting the nutritional needs (use dimension). They suggest that the coverage of food needs can be ensured at the national level by a sufficient supply, but at the local level this coverage will not be sufficient due in particular to the partitioning of the markets and the deficiencies observed at the level of transport infrastructure (accessibility dimension). This could lead some populations to the risk of malnutrition (use dimension). According to the same synthesis carried out by Lankouande and Sirpe (2020), Von Braun (1988) finds that improving the purchasing power (accessibility dimension) of populations most often allows the improvement of their nutritional situation (use dimension). However, sometimes we are dealing with contrasting relationships between the four dimensions of "food and nutritional security (FSN)" is what the researchers describe as Sikasso paradox. Indeed, Mali's Sikasso region is experiencing a higher child malnutrition despite that this region is characterized by a higher agricultural production, which suggests that the relationship between the purchasing power (accessibility dimension), agricultural production (availability dimension) and malnutrition (use dimension) are difficult to identify without ambiguity. All these studies reflect the complexity and ambiguity of the relationship between the four dimensions of the "Food and Nutrition Security (SAN)" and therefore an effort of contextualization and adaptation of study circles is essential to understanding the nature of these relationships (Ouédraogo et al. 2017).

Chiappero-Martinetti and Roche (2009) grouped into four statistical and econometric methods to study the relationships between the four dimensions of the "Food and Nutrition Security (SAN)": the scale solutions and classification theory fuzzy sets, multivariate data reduction techniques and finally the regression approach. In general, these methods have made it possible to decomplexify the study of socioeconomic phenomena (well-being, poverty, human development and inequality). According to Lankouande and Sirpe (2020), the majority of these methods have been used in order to provide aggregate measures of a phenomenon in a numerical value called an index. Indeed, the aggregation of complex socioeconomic phenomena into a single index has gained momentum over the past few years thanks to multidimensional measurement methods. However, this aggregation of data into a single index goes against the multidimensional approach because in the end we reduce the study to a single dimension which is the aggregate index. The first three methods (scale and ranking solutions, fuzzy set theory, multivariate data reduction techniques) are based on this principle of data aggregation and are the most widely used in the empirical literature. Still according to Chiappero-Martinetti and Roche (2009), the fourth group of methods which are the regression methods is most used in the operationalization of the capability approach. These methods allow both aggregated and disaggregated measures and are composed of several models. According to Lankouande and Sirpe (2020), the most used regression models are probit and logit (Burchardt 2005; Ouédraogo et al. 2017) and structural equation models (Krishnakumar and Ballon 2008; Sarr and Ba 2017). Thus, 90% of the studies that used the two forms of the capability approach (operation and capability) were carried out by the regression approach, and the models of structural equations were the most represented (63%) (Chiappero-Martinetti and Roche 2009).

As we have already mentioned above, the structural equation models with latent variables are originally developed by Jöreskog (1973), Keesling (1972) and Wiley (1973) to examine the multiple causal relationships, and their use has extended to construct validity analyses (confirmatory factor analysis) and then to multigroup analyses and longitudinal studies (Lacroux 2009). The main interest of these relational models lies in their ability to simultaneously estimate dependency relationships between several independent latent variables (also called explanatory or exogenous) and several dependent latent variables (also known as to be explained or endogenous). In the structural equation modeling, a latent variable is a variable that is not directly observable and thus cannot be directly measured. On the other hand, a manifest variable could collect a direct measurement. The latent variables are then estimated from the manifest variables by separating them from the common variance.

Indeed, structural equation models are the most suitable for modeling food phenomena approached from the perspective of the capability approach. These socioeconomic phenomena are usually represented by capability areas (capability), with each of them resulting in at least one operation (indicator). Thus, a capability is a combination of a set of operations that is not directly measurable by its functions. Likewise, the dimensions of “Food and Nutritional Security (FNS)” are not directly observable, but each can be understood by a set of indicators. Formally, each of these dimensions (capabilities) is a latent variable in the structural equation modeling, and each latent variable (dimension where capability) is measured by a set of manifest variables (operations). All the operations with their capability (dimension) represent the measurement model, and all the relationships between the four dimensions of the “Food and Nutrition Security (FNS)” represent the structural model.

Thus, structural equations make it possible to better model “food and nutritional security (FNS)” across its four dimensions in a single model. First, they make it possible to calculate the weight of each dimension in determining “Food and Nutritional Security (FNS)”, which allows its dimensions to be ranked according to the context of the study. Second, the evaluation of structural equations’ models is carried out in two phases: evaluation of the measurement model and evaluation of the structural model. The evaluation of the measurement model integrates the two analyses of reliability and validity, which allows a rigorous selection of the indicators (operations) that make up each dimension (capability). The structural model estimates the supposed relationships between the four dimensions which are theoretically not observable.

As we explained earlier, there are several procedures for estimating models of structural equations which differ from each other by the type of algorithm to which they use. However, the two most widely answered procedures in the literature on structural equations are the LISREL method and the PLS method. The PLS method, proposed by Wold (1982), is based on the use of regression techniques in partial least squares that estimates structural equation models. The principle of this method is based on the analysis of variance (Variance-Based Structural Equation Modeling (VBSEM)) and on the optimization of the explanatory power of the indicators.

On the other hand, by difference to the LISREL method which adapts well to confirmatory analyses which suppose the use of a very solid and well-founded theoretical construction, the PLS method is very suitable for estimating models not yet established by theory. In this sense, Jöreskog and Wold (1982) provide "the maximum likelihood method is theory-oriented and emphasizes the transition between exploratory and confirmatory analysis. PLS's primary objective is causal and predictive analysis within the framework of complex models but developed on a limited theoretical basis". Therefore, the PLS method appears to be the most suitable for modeling "Food and Nutritional Security (FNS)" due to the fact that until now the literature used has not made it possible to meet a pre-established theoretical model that has been empirically evaluated showing the links between the dimensions. Another argument in favor of the use of the PLS method is that the majority of models representing food and nutrition security are qualified as partial and exploratory in which it is difficult to constitute a large sample and to have measurement scales (widely proven).

4 Conclusion

Several techniques can be used to estimate the parameters of a structural equation model, which can be grouped under two different approaches: LISREL approach and PLS approach. The LISREL method is based on finding the best parameters to reconstruct the observed covariance matrix of the manifest variables and uses the maximum likelihood estimator which requires multinormality of the manifest variables. However, in social science research, and in particular in studies on "Food and Nutritional Security (FNS)" seen from the perspective of the capability approach, the hypothesis of the multinormality of the distribution of manifest variables harms using the LISREL method. Indeed, since the manifest variables are often population judgments expressed on ordinal scales, they cannot be correctly taken into account, and it is unlikely that they correspond to the multinormal distribution.

In contrast, the PLS approach is based on analysis of variance and does not require the assumption of multinormality of manifest variables. Its algorithm makes it possible to estimate complex models with several variables on small samples, as it also makes it possible to consider more homogeneous contexts and compare the results, and it would be interesting for example to carry out a PLS analysis for separate population groups depending on external variables. Similarly, the algorithm provides a two-level weighting system. Indeed, the results can be interpreted as follows: the structural coefficients represent the impact of exogenous latent variables on the composite indicator (dimension or capability), while the standardized weights are the weights of simple indicators (operations). Together, they define the coefficients of the final linear combinations to calculate the composite indicator (latent variable score). In addition to all these technical considerations and methodologies, the PLS approach is suitable for exploratory approaches that do not require a well-founded theory and allows the estimation of partial models, which is much more consistent with the analytical framework which falls under the "Food and Nutritional Security (FNS)".

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Part III
Nutrition, Human Health and Food Security

Nutrition in Disease Prevention and Food Safety

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Abstract Food safety is ensured when everyone has access to sufficient, healthy, and nutritious food that is adequate to their needs and food preferences for healthy and effective life. It is seen as a causal and related pathway from production through distribution, processing, and consumption. In most instances, the underlying causes of food-related illness are infectious or toxic and are caused by bacteria, viruses, parasites, or chemicals that enter the body through food or contaminated water. Chemical transformation of food constituents can result in either acute poisoning or

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extended illness like cancer, obesity, cardiovascular disease, and mental health disorder. Raw foods of animal origin, fruit, and vegetables, as well as raw shellfish containing marine biotoxins, are examples of unhealthy foods intake. However, creating and exploring data that summarize nutritional intake and its relationship with disease as highly important task in developing disease prevention and curing disease as well. Thus, this chapter highlights recent advances on diseases prevention through food. Also, it describes the association between food safety and contamination during the food preparation process. Developing scientifically sound, innovative, and efficient nutrition involvements is both rewarding and challenging.

Keywords Nutrition · Disease prevention · Food safety · Food contamination

1 Introduction

Nowadays, nutrition and consumer's health become increasingly important. It has led to profound regulatory changes at the national and international levels (Peng et al. 2019). To explore options related to nutrition and health, this chapter focuses on food, and it discusses parts of disease prevention. It highlights both the evolvement of basic food supply and the impact of food processing on human health and nutritional security. It also underlines the fact to survey consumer behaviors to analyze the factors that can negatively affect food processing perceptions. As indicated in the Nutrition HPLE report (2017), a food system includes all elements (environment, population, inputs, processes, infrastructure, institutions, etc.) and activities related to the agro-food chain, as well as the socioeconomic and environmental outcomes. Besides, to meet the global challenge of both nutrition and food security, action should be taken on the quality of the supply fresh and processed food for all people, to ensure that they are suitable and nutritious. Nevertheless, it will also be essential to reduce food waste and to improve food conservation, nutrient content, safety, and shelf life through food processing in a sustainable way. For a world with limited resources, a proportionality between energy content and food composition is fundamental. Environmental sustainability is critical, and the challenge for the agri-food production and processing sectors is to use fewer resources to produce larger quantities of existing. It also contributes to develop new and further innovative foods that are nutritionally, healthily appropriate with long shelf life and are easily transported. Wholesome food patterns that meet the requirements of consumers and are produced by resilient and sustainable food systems must be offered in a changing world of environmental assets reduction.

In the fight against food and nutrition insecurity, it is necessary to integrate a multisectoral focus along the food chain. In addition, the nutritional value of foods can be reduced because of processing techniques and the addition of food additives. This chapter is providing an overview of disease prevention through food and contamination systems. Furthermore, it focuses on the technological aspects of improving the nutritional quality of foodstuffs for the benefit of consumer health and safety. The underlying premise for the study is that for food processing many steps could be sources of contamination like manufacturing processes as well as food transport, cleaning, heating, packaging, and food storage.

2 Disease Prevention Through Food

Obesity, cardiovascular disease, and many other diseases as well as premature mortality can be caused by the consumption of processed foods. Many studies design in different countries show the link between consumption of highly processed food and many diseases (de Deus Mendonça 2018).

The confounding adjusting potential factors related to all three studies explore the fact that the consumption of processed foods increases the mortality risk (Table 1).

The table above shows the interaction between diseases and dietary compounds that can prevent their occurrence. Obesity, cardiovascular disease, and cancer are among these diseases, except that the statistically significant direct association of death specific to the disease has not yet been demonstrated (Rico-Campà et al. 2018).

2.1 *Obesity*

Regardless of age, obesity is a gateway illness that can lead to a fatal health disorder. WHO estimated in 2017 that obesity has reached the proportions of a worldwide pandemic, resulting in the deaths of 2.8 million people yearly. The relationship

Table 1 Components with eventual functions in reducing disease risk

Disease	Prevention-source	Compound
Oxidative stress	Lycopene	Carotene
	Lutein	Xanthophyll
	Quercetin	Flavonol
	Cyanidin	Anthocyanin
	Ubiquinone	Isoprenoid
	Soyasaponin	Triterpenoid
Obesity	β-Conglycinin	Vanilloid
	Capsiate	Protein
	Caffeine	Lipid
	Manno-oligosaccharide	Prebiotics
Hypertension	Acetic acid	Organic acid
Cancer	Chlorogenic acid	Simple polyphenol
	Curcumin	Phenylpropanoid
Diabetes	Neoculin	Sweetening
	Naringin	Flavanone
Hypercholesterolemia	Alginic acid	Polysaccharide
Constipation	*Bifidobacterium lactis*	Probiotics
Osteoporosis	Daidzein	Isoflavone
Detoxification	Sulforaphane	Isothiocyanate
Coagulation	Alliin	Sulfoxide
Hangover	Sesamin	Lignan

between exposure to highly processed foods and obesity-related outcomes in adults has been demonstrated by five cross-sectional and longitudinal studies (Holdsworth et al. 2013; Popkin et al. 2018; Monteiro et al. 2019). Nevertheless, Adams and White (2015) explain that obesity results from the consumption of ultra-processed foods, which has been proven in well-controlled trials.

2.2 Diabetes

Diabetes is the biggest health and medical problem in the world and is evidently associated with lifestyle, especially poor dietary intake (Moghadam et al. 2016). According to the International Diabetes Federation, 463 million people worldwide suffer from diabetes. The commission describes the phenomenon as a real pandemic because it is growing considerably. Likewise, the WHO projects show that 700 million people will have diabetes by the 2045 (Saeedi et al. 2019). Figure 1 shows the overall cumulative effect of type 2 diabetes among food-insecure individuals relative to food secure households.

Consumer's safety presents the primary consideration for human health (Lind et al. 2013), and there is compelling proof that argues for a strong correlation between food safety and physical, psychological, and social behavior (Ohinmaa et al. 2004; Bush et al. 2007).

Through the Fig. 1's graph, coupled with food insecurity, diabetes control becomes a greater and more stressful challenge. Therefore, food-insecure diabetics are struggling with conflicting emphases as food provision and diabetes medication supplies likely to deteriorate their health (Srour et al. 2019).

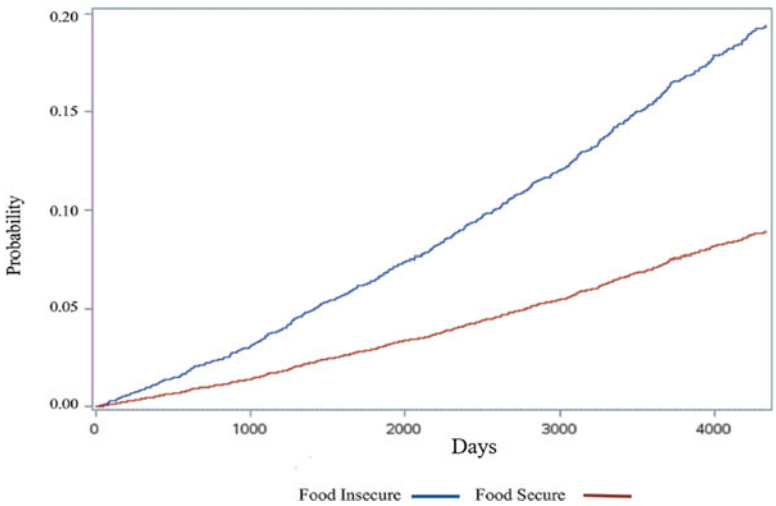

Fig. 1 Cumulative incidence of type 2 diabetes aged 18 or older (Tait et al. 2018)

All health professionals need to be sensitized and knowledgeable of the importance of food security in diabetes prevention and treatment.

However, access to adequate diabetic food does not really ensure food security if quality and food choices are not considered.

2.3 Cancer

Cancer is the second only to cardiovascular disease in the death rate (Siegel et al. 2017; Tilaoui et al. 2019). In 2018, excluding the one notable distinction of non-melanoma skin tumors, 9.5 million people died from cancer (Bray et al. 2018).

Cancer is a multifactorial disease linked with both environmental and biological agents operating either in parallel or in combination, which contributes to the promotion and development of cancers. Overwhelming evidence shows that nutrition factor is associated with many forms of cancers (Burish et al. 2020; Haskins et al. 2020; Tilaoui et al. 2015, 2019; Zyad et al. 2018).

After adjusting for potential confounding factors, significant straightforward relationships were identified for all cancer (excluding prostate and colorectal cancer). This relationship was significant due to total fat, sodium, and carbohydrate consumption. Moreover, both studies show significant evidence of dose-response effects between the level of highly processed foods in the diet and the impact of depression.

Since 2020, timely and cost-effective clinical interventions on nutrition and cancer have been driven by genomic and metabolomic advances. To avoid side effects, it is vital to discover new safe approaches as reducing the posology and/or duration of a medical treatment can affect the therapy by making it less effective than expected, so it is essential to develop new safe approaches.

According to Hackman et al. (2014), Ito et al. (2014), and Furness et al. (2013), Osaka University School of Medicine has been experimenting with two therapies, the first being the use of an active compound correlated to hexose, an extract of shiitake mushroom mycelium, in patients with severe cancer receiving chemotherapy and the second being based on the function of L-glutamine addition to decrease the gravity of mucositis in patients with oral cavity cancer.

2.4 Mental Health

Food insalubrity impacts physical health as well as overall wellness. For instance, there is strong consistency in research findings regarding the negative effects of food insecurity on healthy living. Both depression and anxiety syndrome are frequent mental illness problems that affect our ability to work and of being productive. Worldwide, more than 300 million people suffer from anxiety disorder. More than 260 million have anxiety disorders. Many live with both pathologies (Fitzpatrick et al. 2017). Additionally, a direct phase-response relationship was identified linking processed food consumption and the development of irritable bowel syndrome and functional dyspepsia, which was demonstrated by controlling confounding factors (Monteiro et al. 2019).

3 Food Contamination Along Manufacturing Process

3.1 Food Processing Steps

Several pillars are inextricably involved in the food supply chain, from farmers and processors to manufacturers, distributors, retailers, and consumers. As the diagram of Fig. 2 reveals, the food supply chain is not only complex but also strongly focused and rigorously centralized. This nature maintains many food system key problems including compromised quality and minimal food origin traceability.

3.2 Food Contamination: Origin?

Food contaminants are microbiological and chemical origins, from food production, processing, and packaging. However, raw materials are already contaminated by chemicals due to environmental contamination, industrial growth, agrochemicals, and urban activities that also contribute to ultra-food contamination.

3.3 Food Process Contaminations

In manufacturing of processed food, contamination sources involved are microbiological and chemical origins (Fig. 3).

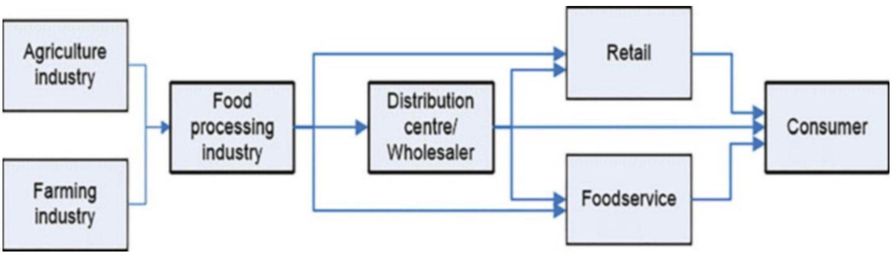

Fig. 2 Food supply chain-general structure

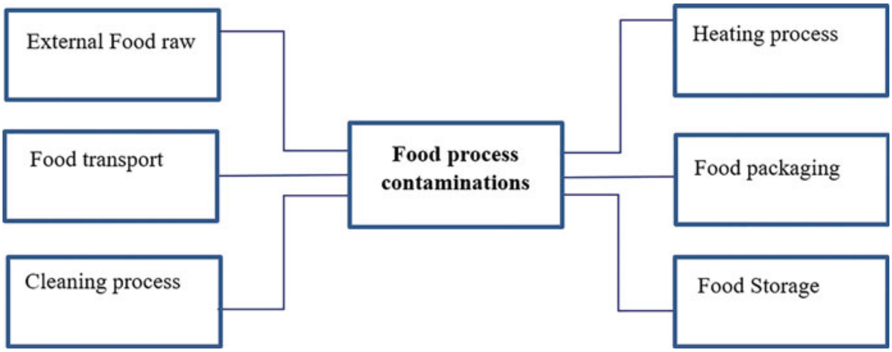

Fig. 3 Food process contaminations

Table 2 Maximum residue limit (MRL) related to animal waste

Antibiotics	MRL (ug/kg)
Gentamicin	200
Tetracycline	100
Oxytetracycline	100
Quinolones	75
Trimethoprim	50
Amoxicillin	4
Ampicillin	4
Nitrofurans	0
Nitroimidazoles	0

3.3.1 Raw Food Contamination

The use of fertilizers and pesticides is a major source of food contamination, since, when consumed by humans, they can cause various illnesses. Environmental contamination can affect raw foods due to certain chemicals present at the food transformation chain outset. Food contamination can also occur from industrial growth, agrochemicals, or urban activities. Many studies have decelerated pesticide traces in vegetable production (Kabayashi et al. 2011) and a few products that have unwanted consequences, like organochlorine pesticides that have been identified in oily foods (Chung and Chen 2011). The chemical compounds application as well as methyl bromide, toluene, ethylbenzene, across a highly protective substance are promoting emission of poisonous metal compounds.

Antibiotic residues are also carefully assessed. These can be unsafe for human consumption if they are outside the acceptable international standards (WHO and FAO). They are used in breeding, but if they are not subject to adequate quality control, they may remain as residual food products. For the analysis of antibiotic substances in commodities (Donkor et al. 2011), various procedures have been established like applying the microplate assay inhibition developed by Koenen-Dierick (1995) or biochemical analysis techniques (Freitas et al. 2014) (Tables 2 and 3).

Table 3 Medical consequences of the antibiotic residuals in foodstuffs

Diseases	Antibiotics
Carcinogenicity	Oxytetracycline, furazolidone
Nephropathy	Gentamicin
Allergy	Penicillin
Bone marrow toxicity	Chloramphenicol

The use of antibiotics in treatment is necessary for animal illness prevention, a retention phase which should be followed till the animal's waste remains no longer detected or negligible. The antimicrobial exploitation with an objective to improve both developmental performance and feed efficacy of the reproductive cycle is often leading to harmful residual effects. This later influences human health by producing potential danger of poisoning. Exposure to antibiotics, even at low doses, would alter the human microflora (Nisha 2008).

3.3.2 Transportation

Food transportation contamination can be caused by exhaust fumes or by cross-contamination in the trucks transporting food. This may set up a severe danger to the food industry's safety. The chemical cross-contamination used for disinfection or from any other sources has in several cases affected transport containers covering long distances (Nerín et al. 2007).

In general, substances with high barrier used for long term transportation packaging food e.g. by shipping are not systematically controlled as the main gases O_2, CO_2 and water vapor that are regulatory monitored at this stage.

3.3.3 Cleaning Process

Chemical products should comply with the requirements of the legislation and be suitable for food-contact surfaces. Cleanup and disinfection, while the food is being processed, remove the presence of microbes and any possible contaminants and are therefore important for the reduction of food contamination. It is therefore essential to quantify the residual chemicals used in food cleaning to certify and ensure that they have been eliminated. Dodecyltrimethylammonium chloride, stearyl alcohol ethoxylate, and non-ionic surfactants are common compounds with quaternary ammonium. Since 1985, Helmschrott et al. investigated factors like flushing time or water temperature that affect the removal of different surfaces of materials affected by disinfectants.

These compounds are typically analyzed by liquid chromatography-mass spectrometry (Vidl et al. 2004; Li and Brownawell 2010). In 2006, also, Naegeli and Kuepper together with several researchers initiated a study on the effects of residues from cleaning agents and disinfectants used in food processing equipment surfaces and their transfer to food that has been in touch with these zones. The food industry must consider the impact of these products on the environment and develop detergent formulations that are safe, effective, and compatible with it. The food-grade utilization and edible surfactants approved by the FDA (Food and Drug Administration) of the United States is an interesting option.

Thanks to its strong oxidizing properties, ozone could be a second alternative. It has been investigated to allow appropriate quality degrees and security. Newly inorganic peroxide combination has also been suggested for this assignment.

On the other hand, a further danger associated with this stage is the compounds alteration by rapid oxidation and the development of new formed products by the interference of food components with disinfection reagents. The interaction between innovative technology trends, electrical impulses impact, raised pressure, and beta and gamma irradiation with food is a new sector in which the food component processing should be studied.

3.3.4 Heat Treatment Effect on Food Properties

To improve palatability, enhance lifetime, eradicate pathogens microbes, and increase sensory quality (Sun 2012), foods are treated thermally. The heating method is usually determined by the type of food matrix, the microbial load, the heating environment, and the final characteristics of product. Currently, several conventional and innovative thermal treatments are used for food processing, mainly pasteurization (Bornhorst et al. 2017), sterilization (Sevenich et al. 2015), canning, and laundry (Malmgren et al. 2017; Datta and Khush 2002). Various heating modes are induction (El-Mashad and Pan 2017), ohmic (Ramaswamy et al. 2014), dielectric radio frequency (Awuah et al. 2014), and microwave-assisted (Guo et al. 2017; Bornhorst et al. 2017), pressure-assisted (Ahn et al. 2007; Wang et al. 2017), and pH-assisted thermal processing (Rana et al. 2021) (Fig. 4).

The toxic compound formation has a negative effect on food quality and safety, and it is due to the combination between high cooking temperature and some external factors. Among those products, acrylamide and nitrosamines may be developed during food transformation. Fried food is the process of cooking that can be used as a source of many food toxic compounds. The oil of fritting process serves as heat transfer support.

d1-3-MCPD

When salted foods meet oil at elevated heat, this gives rise to a new class of heat-induced contaminants, composed of chlorophenol fatty acid esters, like 3-monochloro-1,2-propanediol (3-MCPD) and its derivatives. 3-MCPD may achieve rates over than 14.3 mg/kg. According to a recent EFSA report (2011), the average exposure to 3-MCPD was less than 1 mg/kg daily in almost all population (age groups according to surveys): N ¼ 60 out of 64. 3-MCPD may have different sources and can be produced in acid hydrolysis of some plant protein products

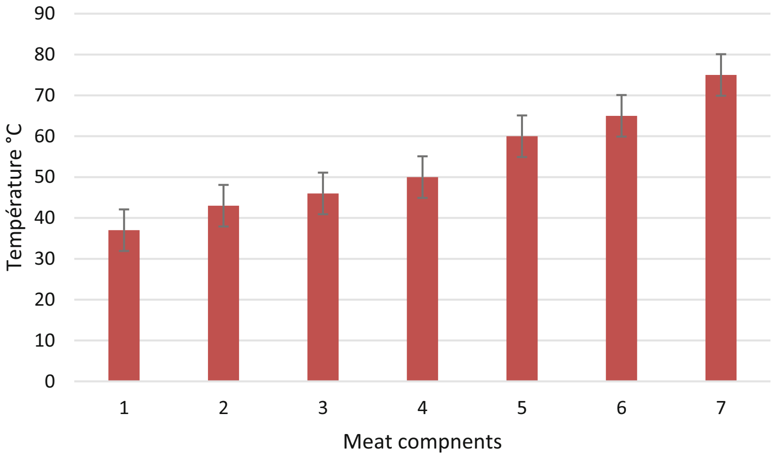

Fig. 4 Variation composition in meat during heat process
(*1*) Fat melting, protein unfolding; (*2*) carbohydrates gelatinization; (*3*) water losses start; (*4*) sarcoplasmic protein, myosin, and actinin denaturation; (*5*) collagen and myoglobin denaturation, fat liquefaction; (*6*) myofibrillar protein aggregation, connective tissue proteins shrinkage; (*7*) titin denaturation

(Johansson and Jägerstad 1993). The EFSA report (2011) suggested the development and establishment of standardized analytical procedures for the 3-MSPD analysis to minimize the occurrence confusion and risk rate (Smidrkal et al. 2016).

d2-Acrylamide

Acrylamide is a highly genotoxic and cancerous agent. It is also the carbon produced in starchy and hydrate-rich foods while handling food at elevated heats. The process of acrylamide requires several factors, the heat transfer is the most important that is an integrated feature of thermal conductivity and heated environment, heating time, water activity, pH and the amino and carbonyl reagents content. Polar components (i.e., pigments) are passed into the frying oil. Nevertheless, acrylamide is also a monomer, with a specific migration limit (SML) in the legislation on food contact plastics. The food's acrylamide concentration derived from heated cereals is unexpectedly beyond the established SML. Numerous efforts were undertaken to decrease acrylamide level in these products, after it was identified that food processing was the predominant source of this component in tremendous food products.

The acrylamide concentration is mitigated by the heat treatment decrease. Not only frying but also baking promotes acrylamide production. A certain mutagenic activity of frying fats is also due to the decomposition products of lipids and hydroperoxides without nitrogen and is independent of the frying substrate. They are due solely to the oxidation products of oxidized and polymerized triacylglycerols or free fatty acids (Nerin et al. 2016).

4 Conclusion

This chapter is particularly meaningful to discard food contamination and, consequently, to reduce potential toxic effects on consumer health. It indicates that food contamination can be produced in the food manufacturing process. Some contaminants may in fact be found in raw materials, though there are many others that may be added during transportation or food transformation caused by a variety of issues like work surfaces cleaning or food heating processes. Furthermore, food wrapping is also a source of contamination. These facts underline the importance of carrying out chemical analyses during food processing to ensure consumers food safety. Heat treatment, on the other hand, produces tremendous alterations in food. These variations have positive and negative impacts on food quality. At present, various thermal techniques are used for food transformation. The improvement of heat treatment techniques is fundamental to achieve food's better nutritional and sensory quality.

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Toxic Plankton Public Health Risks

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Abstract Food poisoning due to the consumption of bivalves has been known for a very long time. Indeed, some toxic microalgal species proliferate excessively under certain climatic and hydrological conditions and cause a harmful algae bloom. However, these species produce phycotoxins that accumulate in the different tissues of shellfish.

Transferred to humans after consumption, these toxins cause various troubles ranging from diarrhea to paralysis according to the nature of these phycotoxins. These phenomena have a significant impact on public health, the economy, and the environment.

In order to prevent these blooms, a monitoring system network has been installed along the Moroccan coasts by the National Fisheries Research Institute (NFRI) to carry out weekly monitoring of toxic species. Seawater samples are regularly taken from several stations. Quantitative and qualitative analyses are carried out on most of the recovered samples.

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This chapter was developed to provide a basic introduction to public health problems that may be related to shellfish consumption and to provide parts of monitoring results for these toxic phytoplankton species of the Oualidia and Sidi Moussa lagoon (Atlantic Moroccan coast) from 2012 to 2014.

Keywords Public health · Harmful algae · Shellfish poisoning · Oualidia lagoon

1 Introduction

Harmful algal blooms are a major environmental problem in the world. The specific composition of phytoplankton communities, the relative abundance of different species, and the dominance of one population over another are all features and phenomena in constant evolution that characterize phytoplankton succession. Indeed, some microalgae produce substances once released, representing a potential risk to the health of the consumer. The Oualidia region is characterized by massive cultures of bivalve mollusks such as mussels and oysters. In this conception, phytoplankton population dynamics are examined through the community's global response to environmental variations using synthetic variables such as total phytoplankton biomass; this approach is essential to understand the inputs of high nutrients in the water lagoons. In this chapter, we adopt the most applied model, that of Mandala of Margalef. It represents the distribution of the different phytoplankton groups under gradients of turbulence and nutrient concentration.

2 Study Area

Sidi Moussa Lagoon

Sidi Moussa lagoon is part of the coastal resort of Sidi Moussa-Oualidia, one of the leading Moroccan wetlands. It is located on the Atlantic coast of Morocco between the towns of El Jadida and Safi about 15 km south of Jorf Lasfar Industrial Park and 41 km south of El Jadida. Its geographical coordinates are between 32 ° 57′ and 32 ° 59′ north latitude and between 8 ° 45′ 8 ° 47′ in the west longitude (El khalidi et al. 2011). Morphologically, we distinguish the presence of three areas:

- A narrow mouth providing a permanent connection with the Atlantic Ocean.
- A substantial sand deposit just inland of the mouth.
- A main channel (maximum depth is 5 m), which runs across a shore with numerous secondary channels (maximum depth is 2 m), decreasing in depth upstream where it is limited by salt marsh.

Oualidia Lagoon

Oualidia lagoon (32°40′42″N-32°47′07″N and 8°52′30″W-9°02′50″W) is located on the Atlantic Ocean (Fig. 1). This lagoon is 7 km long, on average 0.4–0.5 km

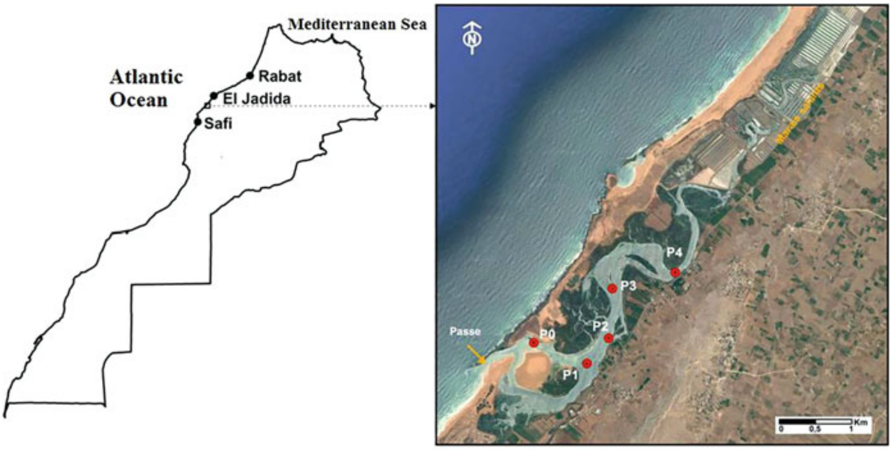

Fig. 1 The geographical location of the Sidi Moussa lagoon and sampling sites

Fig. 2 The geographical location of Oualidia lagoon and sampling sites

wide, and its total area is estimated at 3 km^2 (Beaubrun 1976). In Hilmi et al. (2011), the Oualidia lagoon is characterized by three areas (Carruesco 1989):

- A main pass about 150 m wide, permanent and active all year, and a secondary pass 50 m wide, only active during freshwater tides ensure that the lagoon is continuously connected to the Atlantic Ocean.
- A main channel, the maximum depth of which doesn't exceed 5–6 m, secondary channels (depth maximum 1–1.5 m), intertidal zones, and schorres overgrown with halophyte vegetation.
- An artificial dike separating the marsh lagoon salt (Fig. 2).

3 The Succession of Phytoplankton Assemblages

The succession of phytoplankton assemblages, their behavior in relation to the physicochemical parameters of the environment, as well as their development strategies have been addressed by several authors. The most applied model is Mandala of Margalef.

It represents the distribution of the different phytoplankton groups under gradients of turbulence and nutrient concentration. The combination of these two factors would act in the temporal and spatial regulation of the different morphotypes of phytoplankton, with similar morphology and physiological characteristics.

Margalef describes these groups as having *r* versus *K* strategies. *r* is a fast-breeding species favored by unstable, turbulent environments and relatively high nutrient concentrations (e.g., diatoms). While organisms with *K* strategies reproduce more slowly and dominate more stable environments (e.g., dinoflagellates). Several regions in the world have applied this model to interpret the succession of phytoplankton assemblages, such as in France, in the Bay of Gascogne (Herbland 2012), Brest Bay (Del Amo et al. 1997), and the Odet estuary (Laguerre et al. 2013); and in the Sidi Moussa and Oualidia lagoon complex (the Moroccan Atlantic coast) (current study). In this lagoon system, monitoring covers the four seasons of the year. It can be divided into the following four intervals according to the classical diagram of the succession of phytoplanktonic assemblages (Fig. 3); only species with seasonal variation and high abundances are presented:

- October/November/December: precipitation period/winter.
- January/February/March: the spring transition period.
- Mid-March/April/May: spring bloom.
- June/July/August/September: secondary bloom.

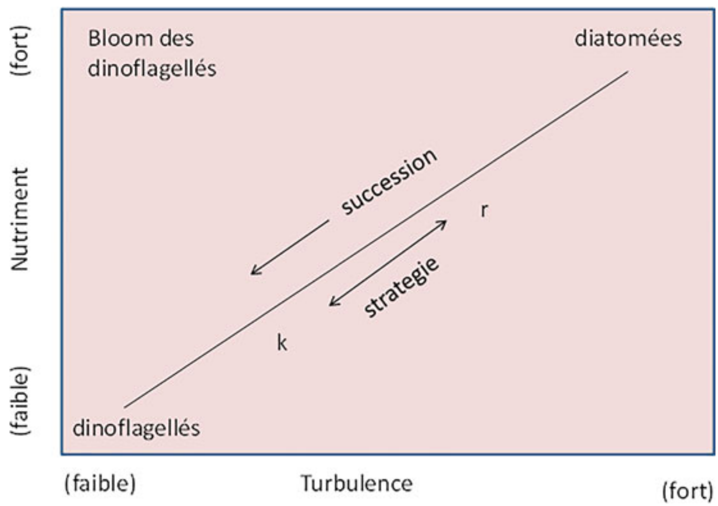

Fig. 3 Conceptual model of the Mandala of Margale. (Source: Margalef et al. 1979a, b)

3.1 Precipitation/Winter

Phytoplankton concentrations are very low in this period, not exceeding 10^4 cell per liter. Specific richness is moderate (an average of 14 taxa). The latter is dominated by diatoms, mainly composed of pennal diatoms: *Pseudo-nitzschia* sp., *Nitzschia* sp., and the genus *Leptocylindrus* sp. However, dinoflagellates are almost absent during this period (with the exception of some presence marked by the genus *Prorocentrum* and *Protoperidinium*). The absence of dinoflagellates during this period is explained by the fact that this group of phytoplankton is less tolerant of turbulence and deep mixing of water, which influences both surface water temperature and brightness (Durham et al. 2009). The same results were reported by Lampert 2001 after a study of phytoplankton dynamics in the North Atlantic (Golfe de Gascogne).

3.2 Spring Transition

During this period, phytoplankton species concentrations and species richness increased slightly, with an average of $4{,}10^5$ C/l and 15 taxa, respectively. Diatoms still dominate the phytoplankton population, including pennal diatoms: *Pseudo-nitzschia* sp. and *Nitzschia* sp. and species forming spring blooms that are starting to appear: *Chaetoceros* spp. and *Thalassiosira* sp., with concentrations of $3{,}10^4$ cells/liter (Del Amo et al. 1997; Laguerre et al. 2013).

During this period, concentrations of nitrates and orthophosphates increased slightly. However, the waters of the lagoon are not so turbid. This proves that diatoms are able to grow more rapidly than other taxa (MartinezGarcia et al. 2010) by having a tolerance to different variations in turbidity (Estrada et al. 1987, 1988). The relative absence of turbulence and nutrient availability are favorable conditions for dinoflagellate development (Margalef 1975; Sournia 1982).

3.3 Spring Bloom

In accordance with the diagram proposed by Del Amo (1997), during this short period "mid-March/April/May," a first peak of dinoflagellate species *Protoperidinium quinquecorne* was noted, accounting for a threshold of $3{,}10^5$ cells/l at station P4 (Daghor 2015). In the same period, a second proliferation of *Chaetoceros* was reported at all sampling stations with concentrations averaging 10^5 cells/liter. However, diatoms still dominate the phytoplankton population presented by central diatoms: *Lauderia* sp., *Rhizosolenia* sp., *Coscinodiscus* sp.

3.4 Secondary Bloom

In this period, a stratification of the lagoon waters was observed; therefore, a massive proliferation was recorded during this period. These blooms are represented by *Scrippsiella* sp., *Ceratium* sp., *Prorocentrum* sp., and *Gymnodinium* sp. with concentrations of 2.10^3, 1.10^3; 10^4, and 2.10^4 Cell/l, respectively; For the diatoms, they are represented by *Pseudo-nitzschia* sp., *Nitzschia* sp., and *Leptocylindrus minimus*. The other peak of this bloom was recorded in June, caused by the dinoflagellate *Kryptoperidinium foliaceum,* reaching a threshold that exceeds 10^6 Cell/l in station P4 (upstream of the lagoon) (Daghor 2015). This result is in accordance with the Mandala of Margalef (1979a, b) model (Fig. 3). Indeed, these conditions (low turbulence and high nutrient concentrations) appear to be perfect for the proliferation of some dinoflagellate species. Indeed, the dinoflagellate species responsible for HAB have a high nutrient affinity coefficient (Margalef 1979a, b; Estrada 1999; Solé 2016) because they have been able to develop adaptive strategies for acquiring these nutrients (Smayda 1997; Gailhard 2003).

These blooms have been identified by several authors and in several countries around the world: in France, brown waters (*Kryptoperidinium foliaceum*) were observed at several locations on the French Atlantic coast during the summers of 1986, 1987, 1988, and exceptionally during the spring of 1991 (E.Nezan 1997), in Tunisia (Turki 2007), in the South Carolina estuary, the United States (Kempton 2002), and in this study (Daghor et al. 2015).

4 Conclusion

This chapter deals with the dynamics of phytoplankton populations as a function of physicochemical parameters and nutrient salts. Two components of the phytoplankton were particularly studied: diatoms and dinoflagellates. The change in the succession of these classes has been linked to major variations in hydroclimatic conditions and the availability of nutrient salts.

This work adopted Margalef's model (Margalef 1978; Margalef et al. 1979a, b), which is considered as one of the most successful conceptual models for explaining the interaction between the physicochemical environment and the phytoplankton community. This model divides phytoplankton into two groups according to their strategy: the "r" strategy characterizing species present during the period of water mixing and high nutrient concentrations, as for diatoms, and the "K" strategy for oligotrophic zones and with stratified waters that characterize dinoflagellates instead.

During the period of this work, two blooms were observed in the Sidi Moussa lagoon. The incriminated species are *Protoperidinium quinquecorne* and *Kryptoperidinium foliaceum* in the period May and June 2013. These blooms coincide with an excessive load of nutrients (nitrites, nitrates, and orthophosphates) especially upstream of the lagoon (station P4). This nutrient enrichment could be explained by the eutrophication of the lagoon and possibly by its proximity to the Jorf Lasfar Industrial Area, which is 15 km away.

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Trace Metals and Food Risks

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Abstract Contamination of food by metal residues remains in the forefront of food security concerns worldwide. The presence of these trace elements in fruits, vegetables, cereals, meats, fish, seafood, shellfish, eggs and milk is the subject of several monitoring plans.

Living beings can be contaminated by these trace metals through their presence in the environment or through the consumption of polluted water and food.

The accumulation of these metals in the living organisms can have harmful effects depending on the type of toxicity.

In this chapter entitled "Trace Metals and Food Risk", we will focus on the exposure routes of the population to trace metals and the negative effects associated with chronical contamination by the latter.

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Keywords Heavy metals · Food security · Food dietary intake · Hazard characterization · Risk Assessment

1 Introduction

In the last few decades, the presence of toxic contaminants in food and water has caused increasing concern from public opinion and health organizations worldwide. Anthropic activities and industrialization in particular contributed to a significant increase in pollutants, which led to an accumulation of contaminants in the food chain. The presence of these toxic elements in the environment and foodstuff at relatively high concentrations can have detrimental effects on the environment and human health.

Food contamination refers to the presence of pathogenic microorganisms in food and also to the harmful chemicals and metals used in agricultural and livestock breeding practices to increase production. Unlike foodborne pathogens, chemical and metallic contaminants in food are often not removed by cleaning and heat treatment. Chemical and metallic contaminants can be classified according to the source of contamination and the mechanism by which they penetrate into the food product.

The contaminants under scrutiny are closely associated with proven as well as potential critical effects on humans. Three categories of contaminants are monitored: environmental contaminants, those associated with inputs used in animal breeding and agriculture, and those associated with a lack of adequate hygiene control over food processing operations. These hazardous contaminants could highly be codified according to the source of contamination and the process through which they enter the food product.

Among these contaminants, heavy metals are increasingly observed in animal source foods (fish and seafood) and plant-based food (fruit, vegetables, and cereals). These metals are naturally omnipresent in surface water; however, their concentrations are generally very low, which explains their denominations as "trace metals" or "metallic trace elements." In addition, they are also produced by anthropic activities, notably industrial and mining activities.

According to a study published in 2015 on food alerts and collective food poisoning as far as food chain monitoring is concerned, the MUS received 952 alerts in France. The distribution of alerts by type of product places meat products at the top of the ranking (40.76%), followed by fishery products (22.58%) and dairy products (17.33%). According to the same study, the five contaminants most frequently associated with product alerts are *Listeria monocytogenes* (32%), followed by *Salmonella* (16%) and heavy metals (9.1%). Additionally, the consumption of fruits and vegetables plays a crucial role in a diversified and nutritious diet. The World Health Organization recommends that we should consume a minimum of 400 g of fruits and vegetables a day to reduce the risk of serious health problems, such as heart disease, stroke, other certain types of cancer, etc.

However, these fresh fruits and vegetables can nevertheless be exposed to contaminants before being consumed. Several epidemiological studies have classified raw fruits and vegetables as the second source of foodborne illness. The consumption of vegetables contaminated with heavy metals can lead to serious human health problems.

Food contains a broad spectrum of metallic elements that are essential in trace amounts for cell functions maintenance at biological, chemical, and molecular levels. Other heavy metals have no functional effects on the body and can be harmful to health if foodstuffs containing them are consumed regularly. The majority of metals are natural components of the Earth's crust (Madkour 2020). Metals and other elements can be naturally present in food or can enter food as a result of human activities such as industrial and agricultural processes (FSAI 2009).

The aim of this chapter is to provide a concise overview of the health hazards due to food metallic contamination. This chapter will deal with mercury, lead, and cadmium.

2 Basic Reminders

Heavy metals are elements having atomic weight between 63.546 and 200.590 and a specific gravity greater than 4.0. They are ubiquitous in the environment; however, their concentrations are generally extremely low, which explains their actual designations of "trace metals" or "trace elements (TEs)."

In contrast to the vast majority of organic contaminants, heavy metals are constituents natural in rocks and mineral deposits. So normally these elements are present at low levels (less than 0.1%) in soils, sediments, surface water, and living organisms (Alloway and Ayres 1997; Callender 2003).

Due to their different specific characteristics, heavy metals are widely used in the field of metallurgy and electronics. As a result, their anthropogenic sources are vast and their introduction into the environment is fairly recent (Callender 2003).

The main anthropogenic source of heavy metals for the environment is that produced by the mining activity and in associated industries, and it has also been identified as one of the first man-made environmental impacts (Nriagu 1996). In addition, the metallurgical industry, fertilizers and pesticides applied in soil cultivation, household waste incinerators, medical waste, emissions from factories, and sewage effluents are also considered anthropogenic sources of heavy metals (Cotran et al. 1990).

The nonbiological essential heavy metals of particular concern in relation to harmful effects on health include mercury (Hg), lead (Pb), cadmium (Cd), tin (Sn), and arsenic (As). Heavy metals can contaminate the ecosystem with industrial waste and acidic rain. Once these heavy metals are bioavailable in the ecosystem, they readily contaminate various foods and subsequently are ingested by living organisms. Heavy metal poisoning could result from drinking water contamination, intake via the food chain, or through the breathing of air contaminated by emission sources of heavy metals.

Some heavy metals are essential trace elements, with functions that are very essential to various biological processes, driving the entire human metabolism. Some heavy metals are essential trace elements, with functions that are very essential to various biological processes, driving the entire human metabolism. Among these elements, some are indispensable, whose absence hinders the functioning or could even prevent the development of an organism. For example, iron (Fe), manganese (Mn), zinc (Zn), and copper (Cu) for plants and animals. In addition, cobalt (Co), chromium (Cr), and selenium (Se) are essential only for animals, while molybdenum (Mo) is a micronutrient for plants (Alloway and Ayres 1997).

3 Routes of Exposure

Most heavy metals are toxic and enter the environment primarily as a consequence of industrial emissions or via disposal of products containing these metals. Soil, water, food, and air are the major exposure media for humans and others living organisms.

3.1 Exposure Through Soil

The heavy metals present in soils are derived from the geochemical reserve, on the one hand, and from the cumulation of anthropogenic inputs, on the other. Soil as a nonrenewable resource, serving as an interface between air and water, is currently faced with complex pollution generated by several human activities, including fertilizing materials, pesticides, and the dumping of wastes and sewage sludge, which involves significant contributions to increasing the concentration of metals in the environment (Granero and Domingo 2002).

Metals can be either fixed in rocks and sediments or mobile. In the first case, the quantities available are extremely small and have no significant effect on the environment. When environmental conditions change in such a way that metals become soluble, the increase in concentration then becomes a direct threat to the environment due to the increase in their availability to living beings. Furthermore, acid rain can increase the mobility of metallic elements in the pores soil by changing its buffer capacity, causing an elevation of their concentrations in agricultural products their concentration in agricultural products**.** Three important origins can thus be distinguished: geochemical background (natural background levels), atmospheric deposition, and anthropogenic inputs (Perrono 1999).

3.2 Geochemical Background

Naturally, the soil contains heavy metals from the bedrock in which it was formed. Thus, soils formed on quartz sands contain extremely low amounts of metals (less than 0.05 mg/kg DM of Cd, less than 5 mg/kg DM of Cu), whereas those formed on calcareous or marly sediments or shales are richer (0.5–1 mg/kg DM of Cd, 25–50 mg/kg DM of Cu) (Perrono 1999). On the basis of a study of 333 soils samples conducted by Pallier, the Ni content of soils is particularly high when the soils have developed on marly or calcareous bedrock (Pailler 1992).

Sedimentary rocks have fairly high levels of trace elements, which increase in the event of fossil carbon accumulation. Notwithstanding this relative abundance in calcareous soils, trace elements are relatively mobile due to the high pH of this type of soil.

3.3 Atmospheric Deposition

The impact of atmospheric pollution on the environment, including atmospheric deposition, is a major concern worldwide. Air pollutants can be emitted in many forms, and their levels of toxicity also vary considerably.

Trace elements eventually deposit on the ground surface depending on wind patterns and ultimately increase their concentrations in adjacent areas.

Atmospheric deposition of these trace elements increases their concentrations in soil and consequently in the food chain (Sharma et al. 2008). The majority of these trace metals are not biodegradable and have effects on food safety (Lim et al. 2005). Heavy metals are released into the atmosphere, usually from anthropogenic sources, including road components, traffic, power plants, industries, and residential heating. To this anthropogenic fallout be added a natural level related to wind erosion of soils and volcanic eruptions.

4 Anthropogenic Inputs

The quasi-totality of the anthropogenic inputs of trace metals is due to the massive use of fertilizer materials, pesticides, and the land application of waste and sludge, and the concentration of heavy metals in soils can increase by repeated and excessive fertilizer and pesticide applications.

4.1 The Fertilizer Materials

These include primary macronutrients, secondary macronutrients, micronutrients, and mixtures thereof. Some types of fertilizers obtained by processing products from mineral deposits contain metal elements that are often much higher than those of the majority of soils. So, the phosphate deposits used in the manufacture of fertilizers are often quite loaded with heavy metals (Perrono 1999). This is notably the case for cadmium, in which the phosphorus content is 70–100% of the metal initially present in the ore (Robert and Juste 1997). The application of these fertilizers can therefore lead to an unavoidable enrichment of cadmium soils. This is also the case for chromium, zinc, nickel, manganese, or cobalt, which, as impurities in fertilizers, are a significant supply source of soil. Equally, the use of traditional organic soil improvers, such as farmyard manure or slurry, will contribute to the increase in content of the heavy metal of the soil.

4.2 Pesticides

Traditionally, the main purposes of the use of chemicals are the enrichment of soil by various nutrient supply (fertilizers) or crop protection against insects and animals (pesticides). Pesticides are substances (chemical compounds and naturally occurring phytochemicals) that are used to kill pests in agricultural as well as household practices (Damalas and Eleftherohorinos 2011). They include compounds labeled as insecticides (organochlorines, organophosphates, carbamates, and pyrethroids), rodenticides (arsenic trioxide, barium carbonate, and anticoagulants), herbicides (paraquat, diquat, and 2, 4-dichlorophenoxyacetic acid), fungicides (dithiocarbamates and captan), and fumigants (ethylene dibromide and methyl bromide).

Recently, metals have found applications in designer chemicals, like agricultural and antimicrobial pesticides. The vast majority of the registered pesticides are organic and are made as fungicide or algaecide or insecticide or rodenticide. A study conducted on glyphosate toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides showed that the sum of heavy metals in formulations after their different recommended dilutions can reach up to 80 ppb. It becomes obvious that the diluted GBH formulations are the most contaminated in general and pose a higher risk of contamination of soils and edible plants, especially in the case of As. Of 11 glyphosate-based herbicides, 6 exceeded the permitted levels in water even after recommended dilutions (1.5–15%) for agricultural or garden uses (Defarge et al. 2018).

5 Exposure Through Water

Supply of safe drinking water is crucial to human life, and safe drinking water should not impose a significant risk to humans (WHO 2011). Drinking water is mainly produced from surface water, groundwater, and desalinating seawater, with desalination satisfying a significant fraction of the drinking water demand in water-scarce regions (Kim et al., 2015). The sources of drinking water are likely to be polluted by heavy metals (Bryan and Langston 1992). Trace metals may be present in aquatic ecosystems as a result of natural processes, especially volcanic eruptions, weathering soils and rocks, as well as from human activities.

The factors affecting the release of trace metals from primary materials and soil and their solution and stability in water are solubility, pH, adsorption characteristics, hydration, coprecipitation colloidal dispersion, and the formation of complexes. As many plants are known to selectively concentrate various metal elements, the concentration of trace metals in the water will be affected and may become available during the decomposition of these plants. Moreover, the corrosion of the distribution system may also increase the concentration of trace metals in water before it reaches the consumer. Lead, copper, zinc, aluminum, and bronze are the elements most frequently encountered at the level of tap water at the consumer level (CSDW 1977).

6 Exposure Through Food

As stated above, there are several routes through which humans can be exposed to heavy metals, including ingestion of contaminated food. Both plants and animals can bioaccumulate heavy metals from the environment within their tissues. Since these plants and animals can be used as sources of food, these heavy metals imply a high risk to human health by expanding many diseases, and that is the reason why most of the major world governments and organizations have studied the effects of heavy metals, primarily lead, cadmium, mercury, and arsenic, on human health. European legislation lays down maximum allowed limits in foodstuffs. EU regulations cover the following heavy metals: mercury, lead, and cadmium.

Mercury comes in elemental, inorganic, and organic forms. Inorganic mercury is converted to organic forms in nature. It is considered to be one of the most toxic metal elements found mainly in fish and fishery products. Methylmercury is the main form in which mercury is present at over 90% than other forms of mercury in fish and other marine animals and in higher amounts in long-lived predator fish. It is easily absorbed into the intestinal system and readily enters the brain, especially the brain of a developing fetus.

Lead is the most commonly used metal. It has entered many agricultural products as chemical fertilizer, herbicide, sewage treatment, and contamination of soil by sewage. This metal is significantly toxic and accumulates in the body, which results in acute poisoning in humans (Tajkarimi et al. 2008). Lead is present at low concentrations in most foods. Offal and mollusks may contain higher levels. Contamination of food during processing or food production in contaminated areas is the main reason for enhanced lead intake viafoodstuffs. The hematopoietic system, nervous system, and renal system are the three main body systems sensitive to this metal (Naseri et al. 2015; Zahir et al. 2005).

Cadmium is an element that can contaminate groundwater supplies, which inevitably affects crops and different animal (Binns et al. 2003). Most foods such as cereals, fruit, vegetables, meat, and fish often have low levels of cadmium. The highest levels of cadmium are found in the offal (kidney and liver) of mammals and in mussels, oysters, and scallops. Certain wild mushrooms may also contain high levels, as can rice grown in certain geological areas where the soil is rich in cadmium. The International Agency for Research on Cancer (IARC) has classified cadmium and cadmium compounds as carcinogenic to humans (Group 1), meaning that there is sufficient evidence for their carcinogenicity in humans (IARC 1993, 2009).

6.1 Food Dietary Intake of Some Heavy Metals and International Recommendations

It is well recognized that some metals such as iron (Fe), zinc (Zn), and copper (Cu) are essential to human health. They are recognized by their role as metalloenzymes and as a cofactor of a large number of enzymes (FDA 2001). Beyond specific concentrations, toxic effects are observed (Singh and Garg 2006). Olalla et al. (2004) have determined that the adequate range for the proper functioning of the body is between 1.5 and 3 mg/day for copper and between 12 and 15 mg/day for zinc. The presence of some heavy metals, like mercury, lead, and cadmium, in the human body even at lower concentration is toxic and draws scientific concern as these are considered responsible for affecting health.

6.1.1 Mercury

The contribution of fish to the total intake of mercury varies from a low of 20% in Belgium and the Netherlands, to a high of 85% in Finland and the United States, with France and the United Kingdom in between (35%) (Galal-Gorchev 1993). In contaminated freshwater areas, mercury levels of 500–700 μg/kg are often found in fish, and in large carnivorous saltwater species such as shark and tuna, it normally falls in the range of 200–1500 μg/kg. Levels in fish from unpolluted waters are found to vary, but not exceeding about 200 μg/kg, and levels in mollusks and crustacea are rarely above 100 μg/kg. For grains, cereal products, vegetables, fruit, and meat, several studies have shown that mercury levels are generally below 30 μg/kg (UNEP 1992).

For mercury, a provisional tolerable weekly intake of 300 μg per person (equivalent to 5 μg/kg of body weight) has been established, of which no more than 200 μg (3.3 μ/kg) should be methylmercury for the general population, but it is important to note that pregnant women and nursing mothers are likely to be at greater risk from the adverse effects of methylmercury. The available data were considered insufficient to recommend a specific methylmercury intake for this population group (UNEP 1992; WHO 1989).

6.1.2 Lead

The average dietary intake data of lead by adults between 1980 and 1988 in 25 countries ranged from 1 to 63 μg/kg bw/week. In this period, the intakes slightly exceeding or approaching the provisional tolerable weekly intake (PTWI), which is of the order of 50 μg/kg bw/week, were reported for the average adult in Cuba, India, Italy, and Thailand. The lowest intake was reported by the United States. Furthermore, the lead intake for "extreme" adult consumers in Australia was about 17 μg/kg bw/wk. (approximately four times the intake of the "average" adult). Similarly, a mean intake of 25 µg/kg bw/wk. was reported in New Zealand. In Denmark and the United Kingdom, the average adult weekly intake was 8 µg/kg bw and 7 µg/kg bw/wk., respectively. In the monitoring program, emphasis was placed on staple foods such as cereals and potatoes and on foods that are most likely to contain high levels of lead (canned food, shellfish) (Galal-Gorchev 1993).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable weekly intake (PTWI) for lead of 50 µg/kg of body weight to adults (WHO 1978). A guideline value of 0.05 mg/liter has been recommended for lead in drinking water (WHO 1984).

6.1.3 Cadmium

The national regulatory limits for cadmium from all sources from 31 countries vary from 10 µg/kg in milk or eggs to 2000 µg/kg in fish and shellfish, and the established PTWI is 7 µg/kg body weight. With the exception of Thailand, all reported intakes are below the PTWI of 7 µg/kg bw (UNEP 1992).

Cereals and their products, followed by potatoes and other vegetables, are ranked as the largest contributors to intake of cadmium in Canada, Denmark, Finland, the Netherlands, and the United States. The little intake contribution of this metal element is provided by fruit, meat, poultry, and dairy products (Galal-Gorchev 1993).

The JECFA has established a PTWI of cadmium of 7 µg/kg bw, applicable to adults as well as infants and children. A guideline value of 0.005 mg/liter has been recommended for cadmium in drinking water (WHO 1984).

6.2 Hazard Characterization and Risk Assessment

The data in this part are based on the French Total Diet Study conducted by the French National Institute for Agricultural Research (INRA) between 2000 and 2004 on 338 food items (Leblanc et al. 2005).

6.2.1 Mercury

Current epidemiological data strongly suggest that methylmercury is a neurotoxic substance responsible for delayed psychomotor development in children. With a view to providing an additional precaution regarding the potential impact of methylmercury on the neurological development of the fetus, the JECFA reevaluated the provisional tolerable weekly intake (PTWI) in 2003, lowering it to 1.6 µg/kg body weight (WHO 2003).

In terms of risk assessment, 38% of the samples analyzed showed mercury levels above the limit of detection (LOD) of 6 mg/kg of fresh weight.

The food groups that have shown significant mercury levels are the fish group and the chocolate group with mean values of 62 μg/kg and 42 μg/kg mg, respectively. The other food groups contain less than 17 μg/kg.

6.2.2 Lead

Lead is a cumulative toxicant that affects multiple body systems. It is particularly harmful to the system hematopoietic, nervous system, kidneys, and male reproductive system. In addition, several studies have shown that the major toxic effect of lead during the development of fetus can cause lasting neurobehavioral deficit in childhood. In 2000, the JECFA confirmed the provisional tolerable weekly intake of 25 μg/kg body weight (WHO 2000).

According to the same study, 75% of the samples analyzed show levels of lead above the limit of detection (LOD) of 5 μg/kg of fresh weight. Lead is found present at an average level between 0.05 and 0.1 mg/kg for the organ meats group and shellfish, and the other groups mainly present levels less than 0.04 mg/kg.

6.2.3 Cadmium

The International Agency for Research on Cancer (IARC) has classified cadmium and cadmium compounds as carcinogenic to humans (Group 1), meaning that there is sufficient evidence for their carcinogenicity in humans (IARC 1993, 2009).

The cadmium accumulates primarily in the kidneys, and its biological half-life in humans is between 10 and 30 years (WHO 2008). This accumulation may lead to irreversible renal tubular dysfunction, which results in increased excretion of low molecular weight proteins in the urine. The provisional tolerable weekly intake is confirmed by the JECFA in 2003 at the level of 7 μg/kg body weight (WHO 2003).

Still referring to the same study, 31% of the food samples display cadmium levels < LOD of μg/kg of fresh weight. Cadmium is found at an average level between 0.05 and 0.1 mg/kg in offals and shellfish; the majority of other food groups contain less than 0.02 mg/kg.

7 Conclusion

Because of the large production and immoderate consumption, the worldwide practice has exposed consumers to carcinogenic and pathogenic risks from contaminated foodstuffs. Heavy metals are considered toxic substances and persistent pollutants that are still found throughout the Earth's crust, posing risks to ecological and human health. In fact, exposure to heavy metals brings potential threats for major diseases such as neurotoxicity, infertility, risk of diabetes, immune suppression, risk of cardiovascular disorders, renal damage, birth defects, and cancer. The sources of heavy metals in food crops necessitate specific attention to determine the actual metal toxicity. In different countries, the current situation analysis of trace metal contaminations leads to conclude that there are hotspots suffering from agrochemicals and domestic wastes such as fertilizers and pesticides.

As they are nondegradable, appropriate methods need to be established for their efficient removal from the environment. Furthermore, to ensure a complete understanding of disease pathology likewise molecular and cellular pathways involved in this regard, more risk assessment research and comparative concentrations to international standards set for humans and ecosystem health are required.

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Protein Diet and Management of Hepatic Encephalopathy: An Overview of the Last Decade Controversy

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Abstract Hepatic encephalopathy (HE) is a brain disorder that takes place subsequently to liver insufficiency or portosystemic shunting. Patients with HE show a mild cognitive and motor impairment and present a high level of systemic ammonia, which is believed to be the main factor setting of the central nervous system (CNS) complications. The gut microbiota increase furthermore ammonia levels in the

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systemic circulation, especially under the circumstances of liver insufficiency. Moreover, a protein-rich diet, especially originating from animals, is shown to precipitate HE, a postulate that roots back to the first researches of Nencki and Zaleski. Thus, protein diet management has long been thought to act as a crucial factor in the management of hyperammonemia and inflammation in patients with HE. Up to the last decade, the research advancement on the dietary management of liver diseases and HE was very controversial; is it better to take or avoid a protein-rich diet? This chapter is a review of the most relevant evidence revealing the importance of protein dietary management on the treatment of HE.

Keywords Hepatic encephalopathy · Brain-disorder · Liver · Cognitive and motor impairment · Ammonia · Central nervous system · Gut microbiota · Protein diet management · Hyperammonemia · Inflammation

1 Introduction

Hepatic encephalopathy (HE) is a serious brain complication developed from liver diseases. It is characterized by an array of neuropsychiatric and neurological symptoms. These include fine motor, psychomotor, and neurocognitive functions perturbations, in addition to discrepancies in attention, visual perception, and visuospatial construction. Based on a battery of neuropsychiatric tests named the West Haven criteria, HE is categorized into four grades. Grade I patients present a reduction in their attention span and sleep disorder. This is developed into personality changes, disorientation, and asterixis in grade II patients, followed by confusion and semi-stupor characterizing grade III, all of which are reversible subclinical changes after recovery. Nevertheless, grade IV of HE is typified with irreversible comatose, which may lead to death. Indeed, the burden of HE is increasing with a prevalence of 10–21% overt expression, with considerable effect on patients' and caregivers' quality of life (Butterworth 2020).

The interaction between the liver and gut microbiota has shown great evidence. The liver's metabolites, especially the bile products, have antimicrobial action upon the gut bacteria via the bile and portal secretion systems (Begley et al. 2005), maintaining a state of bacterial homeostasis within the intestine. In liver dysfunction, such as the case in cirrhosis, the immune system abnormalities and intestinal barrier impairment lead to intestinal bacteria (overgrowth) dysbiosis and gut bacteria translocation (Muñoz et al. 2019). Conversely and interestingly, extrinsic factors, especially diet-related factors (Tomasello et al. 2016), contribute to similar changes in the gut microbiota, with disrupted intestinal homeostasis, which lead to a wide spectrum of liver diseases such as nonalcoholic fatty liver disease, steatohepatitis, alcoholic liver disease, and cirrhosis (Schnabl and Brenner 2014). Such interaction has made clear the interplay between liver diseases, and gut dysbiosis and bacterial translocation through the gut–liver axis, and between the liver and the brain via the gut–liver–brain axis.

Hence, the development of HE among patients with liver failure is obviously associated with malnutrition, such as in cirrhotic patients (Reuter et al. 2019). The dietary management of liver diseases and HE has since gained increasing importance. Previous researches put the line on protein of animal origin privation for HE patients, suggesting that this may improve their state. Nevertheless, recent findings have better suggested normal protein intake (Córdoba et al. 2004) and equilibrated diet with adequate amounts of protein, carbohydrates, and fat (Amodio et al. 2013; Merli et al. 2019). In this chapter, we review the role of the gut microbiota in the pathogenesis of liver diseases and HE. Then, we shed light on the adequate diet management strategies as suggested by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) (Amodio et al. 2013) and the European Association for the Study of the Liver (EASL) (Merli et al. 2019).

2 The Intestinal Flora

The intestinal flora, also called gut microbiota, refers to the sum of microorganisms colonizing the digestive tract and living in harmony with the host. The human organism contains more than 100,000 billion bacteria, which multiply a hundred times the host's own eukaryotic cells. For a long time, microbiota had been thought of as a unique digestive role, especially through the fermentation of fibers. Then, recent research data revealed a truly more complex ecosystem, which potentially has its own means of communication with the entire organism (Raubenheimer and Simpson 2016). Based on their influence upon the host, this ecosystem is mainly composed of bacteria classified into three types of flora: (1) symbiotic bacteria with a beneficial effect on health; (2) commensal bacteria, which applies neither beneficial nor bad influence; and (3) opportunistic bacteria, which have the potential to multiply and become pathogenic for the host following changes in the environmental conditions, especially the nutritive intake (Relman 2012).

Several functions are fulfilled by the intestinal microbial ecosystem through their large mutual symbiotic relationship with the host. As this last provides a niche with stable conditions of pH, oxygen, temperature, and nutrients, the microbiota implement several pertinent physiological functions in return. These range from digestive, immune, and metabolic to regulatory functions upon several systems among which the central nervous system (CNS) is importantly concerned. Several studies have put the line on the multiple physiological implications of the gut microbiota. In this chapter, we focus on the effect of ammonia on the gut–brain axis to stretch the understanding of the links relating HE to intestinal dysbiosis.

3 Protein-Related Dysbiosis and the Gut–Liver–Brain Axis

Dysbiosis refers to a quantitative and qualitative disruption of the gut microbiota causing a loss of its diversity. This leads to an imbalance where especially opportunistic bacteria take it over the symbiotic bacteria. The alteration of bacterial

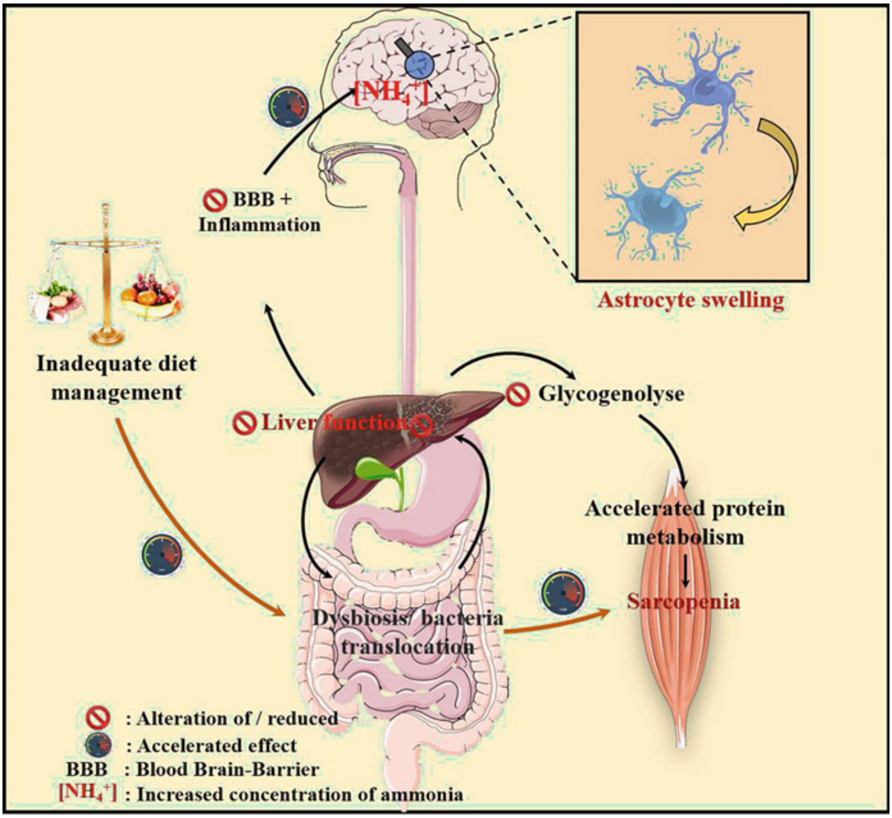

Fig. 1 Overview of the consequences of gut–liver–brain axis alteration

diversity may promote many disorders, and especially in the cases of hepatic insufficiency, it can play as a precipitating factor of HE (Shawcross 2015). Overt HE is often precipitated by gut-related conditions such as infections, increased protein load due to acute upper gastrointestinal bleeding, constipation, and drugs such as opioids that slow the intestinal transit. Several pieces of evidence have revealed a link between cirrhosis and the alteration of microbiota, which indeed could show a positive correlation with the progression and complications in the severity of cirrhosis (Muñoz et al. 2019). In particular, this alteration shows its associations with infections, factors that lead to sepsis and death (Fig. 1).

The gut-produced nitrogenous compounds are among the most potential precipitating factors in HE, as in the case of rich nitrogen food intake (Battson et al. 2018). This refers back to the first postulate by Nencki and Zaleski, who found out that dogs with portocaval shunts develop HE only if they are fed with meat. While in the control case where the provided food is bread and milk, the portocaval shunt does not set off complications of HE (Nencki et al. 1895). Recently, several clinical postulates have shown that a protein-rich diet develops HE in the case of patients with hyperammonemia and inflammation. Nevertheless, patients with hyperammonemia only do not develop HE. There has been a strong correlation between HE and the concentrations of circulating tumor necrosis factor alpha (TNFα) in cirrhotic patients. Thus, the implication of inflammation mediated by TNFα in the appearance of neuropsychiatric effects related to hyperammonemia in patients with HE is obvious (Tivers et al. 2014). Though the interaction between inflammation and hyperammonemia is obviously relevant, the precise mechanism by which they lead to HE is unclear so far.

The mechanism leading to hyperammonemia has sharply been defined (Fig. 1). In patients with acute liver diseases, such as hepatic necrosis, patients develop HE rapidly because of the decreased urea cycle within the liver. This increases the endogenous ammonia that readily crosses the blood–brain barrier. In the CNS, only astrocytes have the ability to detoxify ammonia using glutamine synthetase, which increases the produced glutamine in their cytosol causing astrocyte swelling (Tapper et al. 2015). In roughly 25% of liver disease cases, this leads to intracranial hypertension and brain herniation (Bernal et al. 2007). However, when cirrhosis is the leading cause of HE, hyperammonemia may not have such a strong implication in the precipitation, and increased levels of ammonia are relevant though. Recent shreds of evidence may support this through the poor correlation revealed between blood ammonia concentrations and the severity of HE. In fact, liver infection and gut bacteria dysbiosis may exacerbate inflammation and act synergically with hyperammonemia in exacerbating HE (Shawcross et al. 2011).

The immune response of the liver plays a pillar role in neutralizing bacteria and toxins absorbed from the gut. In the case of dysbiosis, the change in the mucosal barrier integrity leads to bacterial overgrowth and translocation, thus delivering bacteria through the portal vein (Fig. 2). This activates macrophage that recognize bacterial-derived lipopolysaccharides as well as other bacterial by-products, leading to the production of TNFα and IL-8. Such pro-inflammatory responses drive the activation of hepatic infiltration of monocytes and neutrophils, resulting in hepatic inflammation and injury. Moreover, the overlay of exuberant systemic inflammation in cirrhotic patients is well documented (Knott 2020).

It has been shown indeed in patients with cirrhosis or portosystemic shunt an escape of the bacterial degradation products because of the gut wall permeability, consequently enhancing systemic endotoxemia and immune dysfunction, such as reduced monocytes activity due to a decrease in the expression of their HLA-DR in patients with decompensated cirrhosis. Importantly, hyeperammonemia has itself shown evidence of reduced phagocytic activity, neutrophils' swelling, and increased oxidative stress (Shawcross et al. 2008). Moreover, a synergic interaction between hyperammonemia and inflammation has recently been suggested to alter the blood–brain barrier (BBB), increasing its permeability in animal models (Mouri et al. 2017). This may explain the imagery results showing vasogenic edema in patients with HE (Anderson et al. 2020; Hinchey et al. 1996). Such facts being evident, they altogether give insight into how a synergetic effect between hyperammonemia and inflammation may set off the precipitation of HE.

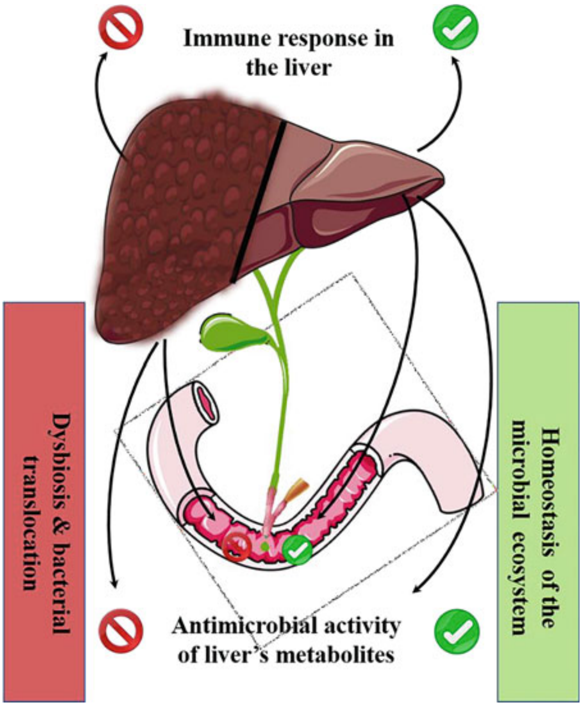

Fig. 2 Liver dysfunction-induced immune system dysfunction and gut dysbiosis

Therefore, it is of interest to put the line on the relevance of targeting the gut in the therapy of HE since increasing evidence suggests that dysbiosis, bacterial overgrowth, and exacerbated bacterial translocation are among the original causes of inflammation and hyperammonemia. Several gut-targeting therapeutic strategies have long been approached. In the following section, we will update the most pertinent diet management strategies of HE.

4 Gut Microbiota, a Key Therapeutic Target of HE

As the implication of hyperammonemia and inflammations is forcefully suggested to be a cutoff in the pathogenesis of HE, the main current therapeutic strategies focus on reducing ammonia production and absorption from the gut (Alsahhar and Rahimi 2019). It has been supported that the colonic bacteria are the primary source of generated ammonia from splitting urea and amino acids. Hence, nonabsorbable disaccharides (lactulose and lactitol) have been used to reduce the production of ammonia. Nonabsorbable disaccharides indeed reduce pH in the colonic environment, which therefore creates a hostile environment for the urease-producing bacteria, and reduce absorption of the colonic acid secretions. Such treatment has been a main stay in the therapy of HE. Moreover, the results of treatment with lactulose have shown increased quality of life, especially in patients with mild HE (MHE). Nevertheless, in patients with cirrhosis and acute HE (AHE), this has shown no advantage upon reducing mortality (Als-Nielsen et al. 2004). It was additionally considered to be used in antibiotics such as neomycin, metronidazole, and vancomycin in order to reduce the gut microbiota so that the production of ammonia will be reduced. Nevertheless, such treatment has revealed long-term side effects, such as peripheral neuropathy, ototoxicity, and nephrotoxicity.

Moreover, reducing inflammation has interestingly shown efficacious results in reducing HE. Thus, it has been suggested to focus on pharmacotherapeutic strategies targeting the evolution of bacterial translocation, endotoxemia, and immune dysfunction. Such therapeutic strategies may include pre presymbiotic treatments, all with selective decontamination of the intestine with nonabsorbable, nontoxic antibiotics (Shawcross 2015). Several other therapeutic approaches not targeting the gut microbiome have shown good results. Nevertheless, they are out of this review's focus.

The therapeutic approaches have importantly reduced the burden of HE upon patients and caregivers. However, adequate therapy should be accompanied with personalized diet management. The supply of ammonia being mainly of a nutritional origin, the dietary management of HE is likely the most rational following step to focus on in the prevention of HE.

5 Nutritional Issue in HE

Several clinical data have brought up the need to assess the nutritional statement of patients with cirrhosis and HE. In fact, malnutrition, sarcopenia, and weakness are frequently interwoven conditions in cirrhosis, which are additionally associated with impaired muscles' health.

Muscles are a considerable source of ammonia that act via disposing glutamine. Therefore, muscle wasting is highly associated with HE, including cases of patients with transjugular intrahepatic portosystemic shunt. Indeed, the state of hyperammonemia itself decreases protein synthesis in the muscle and causes autophagy because of its direct toxic effect and upregulation of myostatine. When malnutrition sets as an additional factor, this precipitates more the muscle breakdown, a case that is amplified in cirrhosis where the hepatic glycogen depletion leads to a shift to protein catabolism, especially proteins of the muscles to meet the needs of neoglucogenesis. In fact, the impaired hepatic glycogen synthesis and storage leads to reduced glucose utilization, which affects as well the macronutrients' utilization (Owen et al. 1981). Consequently, patients with cirrhosis present a reaction to fasting similar to this of starvation in healthy individuals, such as quick and more excessive activation of lipolysis, with the utilization of fat reserves, and a shift from glycogenolysis to gluconeogenesis (Krähenbühl et al. 2003; Petrides et al. 1991). Gluconeogenesis is a procedure that wastes too much energy, which may explain the observed lean body mass and increased resting energy expenditure of patients with liver cirrhosis (McCullough and Raguso 1999; Müller et al. 1999).

Personalized assessment of patients' nutritional statute is therefore a preliminary procedure in the treatment of patients with HE. As HE has been suggested to not have any metabolic cost, present consensus recommends a minimum 35 kcal/kg body weight per day in the nonobese and dietician-guided intake in the obese. As for adequate daily protein uptake, the guideline recommended 1.2–1.5 g/kg body weight per day and to avoid fasting for more than 3–4 h with attention given to a late evening and early morning protein- and carbohydrate-containing meal/snack.

6 To Take or to Avoid the Protein-Containing Meal, What Is Better for Patients with HE?

Proteins are essential as an energy supplier and are a vital source of nitrogen for the gut bacteria requiring it. The metabolism process of proteins starts by hydrolyzing it into small peptides through protease activity. The peptides are then turned over into amino acids, which will serve either as a source of energy for bacteria unable to ferment carbohydrates or to provide nitrogen (Rowland et al. 2018). This peptide metabolism takes place in a process of deamination that produces short-chain fatty acids and ammonia. Among the metabolic products of protein are the aromatic chain amino acids, mainly phenylalanine, tyrosine, and tryptophan, of which the decarboxylation pathway leads to the formation of phenolic and indolic compounds (Smith and Macfarlane 1997). These may have a potential toxic effect but are absorbed and detoxified by colonic cells to be excreted in the urine. Concerning the resulting ammonia, it could serve as a source of bacteria that turn it over into amino acids and proteins. Otherwise, this may reach the liver via the portal circulation where it integrates the urea cycle, and then gains the elimination path to urine.

Nitrogen metabolism is indeed significantly implicated in the pathogenesis of HE, especially in patients with cirrhosis. The need to understand the mechanisms implicating proteins in the pathogenesis has been a critical issue in the last decades, especially because this has created ambiguity within researchers on the adequate procedure in managing protein intake for patients with HE. Early clinical studies have shown that reducing protein intake might control periods of OHE among cirrhotic patients (Riordan and Williams 1997). Then, in 2004, Cordoba et al. published the first prospective, randomized controlled study of cirrhotic patients that were given different amounts of dietary protein. The results suggested that protein restriction is of any beneficial contribution for patients' amelioration (Córdoba et al. 2004). Even though the study has been criticized for inadequate randomization and not taking into account the protein sources (Nguyen and Morgan 2014), it consistently revealed the evidence on the interest of dietary management of proteins. In fact, though protein has been recognized as a key to the prognosis of HE, its uptake management is a poorly understood aspect and remains a subject with little agreement and poor standardization.

Cordoba et al.'s study has indeed shed light on the interest of a potential protein diet management on the amelioration of patients with cirrhosis and HE. Consecutive studies have then associated nocturnal snack intake [15% (26 g) protein, 53% carbohydrate, and 32% fat] to improved nitrogenous balance, improved body protein store, and ameliorated quality of life (Plank et al. 2008). So far, more focus has been put on the effectiveness of dietary support in the amelioration of the patients' health. One study with a randomized trial of nutritional management in cirrhotic patients with minimal HE has shown amelioration of neurocognitive functions and quality of life, as well as reduced hospitalization (Maharshi et al. 2016). Moreover, a study with retrospective and prospective phases comparison has shown that the nutrition assessment of cirrhosis in patients shows improvement, which thus reduced the risk of patients' inherent sarcopenia and HE (Reuter et al. 2019). This study has also valued the nutritional recommendations proposed by the ISHEN (Amodio et al. 2013) and the EASL (Merli et al. 2019).

From a practical view, it is advised to balance diet intake of fat, carbohydrate, and protein referring to the geometry of nutrition concept (Raubenheimer and Simpson 2016). Thus, to respect such balance and reduce food boredom, it is suggested to diversify the protein sources, taking not only vegetable proteins such as beans and tofu, but also meat, dairy proteins, meal supplements, and protein powder. The evidence supporting nonmeat diet in liver diseases leading to HE is week indeed.

7 Conclusion

In conclusion, liver dysfunction is often related to gut dysbiosis, which leads to inflammation and hyperammonemia. Thus, it is highly suggested to avoid dietary imbalance in patients with liver diseases so that they will maintain their muscular mass and prevent HE. It is a matter of great evidence in the management of liver diseases to maintain an equilibrated diet with the recommended amounts of proteins, carbohydrates, and fats. Therefore, it is of great interest to put more focus on the dietary management of HE as to come out with more effective preventive and therapeutic strategies.

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Nutritional Diet and Health Among Moroccan Childbearing Women

Saloua Lamtali

Abstract In a woman's life occurs hormonal and physiological changes that affect her nutritional status. So, adequate nutrition is a basic need for her good health. In Morocco, there are, in parallel, nutritional deficiencies, especially in micronutrients like iron, and problems of excess like obesity. This is the double nutritional burden faced by many developing countries. The rates of obesity among women aged 20 years reached 21% and 30% of overweight. In this context, we have conducted studies about diet and nutritional status among women of childbearing age, in Marrakesh, and assessed health complications due to obesity. Results showed a high incidence of complications in obese women during pregnancy, childbirth, and postpartum. Also, overweight and abdominal obesity may be responsible for infertility for women to whom there is no diagnosed cause of infertility. We have noticed a low adherence to the Mediterranean diet qualified as a healthy diet.

These emerging nutritional disorders are related to urbanization and changes in lifestyles and nutrition, and they can cause many health and economic consequences. Therefore, it creates new challenges for the national health system. More efforts are required to develop a comprehensive nutritional policy in Morocco.

Keywords Nutrition · Overweight · Obesity · Women · Childbearing · Infertility · Pregnancy · Morocco · Marrakesh

1 Introduction

Changes in diet, habits, and lifestyles of human populations (nutritional transition), observed over the last decades, have contributed to an increase in overweight, obesity, and some chronic diseases associated with nutrition (WHO 2018). According to recent WHO global statistics, more than 1.9 million adults were overweight and 600 million were obese; globally, 10% of the world's adult population were obese. Generally, female population is more affected, when 15% of obese women versus 11% for men were reported (WHO 2018).

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In Morocco, the demographic transition has been accompanied by changes in lifestyles, including food and physical activity (HCP 2010). This nutritional transition was marked by the transition from a traditional diet based on cereals and vegetables to a diet that includes more animal products and tends to become excessive in relation to the energy needs of a sedentary life (Lamtali et al. 2016).

In the goal to approach should be integrated into the health-care system, especially among women of child bearing age.

In this context, we have conducted studies about diet and nutritional status among women of childbearing age in Marrakech, Morocco. Also, we have investigated health complications due to obesity among these women. This study would provide elements for the health system in order to integrate the dietetic approach in any women care.

In the following, three subjects will be presented:

- Obesity and pregnancy
- Adherence to Mediterranean diet
- Infertility and nutrition

2 Obesity and Pregnancy Among Moroccan Women Introduction

According to national statistics, more than 10 million Moroccan adults are obese or preobese (nearly one in three Moroccans) (HCP 2010). 63.1% among them are women, including women of childbearing age (Moroccan Ministry of Health MMH 2011). Obesity is responsible for significant complications among pregnant women, and it can put their health, as well as their newborn's, at a major risk (HCP 2010; MMH 2011). Indeed, during pregnancy, obesity increases the risk of maternal complications (gestational hypertension, gestational diabetes) and fetal complications (malformations, macrosomia). The conditions of delivery are also more difficult, with more caesareans and failures of epidural analgesia (Djorolo et al. 2002, Galtier et al. 2005, Bringer et al. 2008).

The objective of this original study was to describe the complications linked to obesity in pregnancy, childbirth, and postpartum among Moroccan women.

2.1 Materials and Methods

Study Area This cross-sectional quantitative descriptive study was conducted in 2017 in Marrakech city. Data were collected in the maternity services of the University Hospital Center, Mohamed VI (CHU, MVI), and at the maternity of Ibn Zohr Hospital.

Population A sample of 200 women was included in the study according to an accidental probabilistic sampling based on two major inclusion criteria:

- Women had just given birth and thus had an experience of pregnancy, childbirth, and postpartum.
- Women with a body mass index (the weight before pregnancy) more than 30 (BMI>30).

Data Collection Standardized interviews were used for data collection from eligible participants. The interview questions were tested among 10 women who were excluded from the main study sample. We collected information about women's sociodemographic status and complications occurring during pregnancy, childbirth, and postpartum experience. Our data were completed and confirmed from official participants' birth records.

Ethical Considerations Before starting our study, we received approval from the local ethics committee of the Ministry of Health. All participants were informed by the objective of the study and gave their free informed consent to participate in the study.

Data Analysis Data were analyzed by the SPSS software (version 10). We calculated the means and standard deviations for the quantitative variables and the frequencies and percentages for the qualitative variables.

Women's body mass index was calculated according to BMI = weight (kg)/size^2 (m) with the weight of women is before pregnancy.

2.2 Results

In total, 200 women participated in this study, aged between 18 and 43 years with a mean age of 29.75 years (SD = 7.6). The demographic origin is rural for 51% (N = 103) of participants, and more than 75% (N = 150) of them were illiterate or did not exceed the level of primary instruction at the moment of the survey. More than 94% of the participants did not have any professional activity. Also, 43% did not have health insurance, and for those who were insured, more than 90% had RAMED (Medical Assistance Plan) (Table 1).

The BMI of participants ranged from 30 to 48.65 with an average of 34.51 (SD = 3.63). The distribution by grades of obesity showed more than 37% of severe obesity and morbid obesity among participants (Table 1).

The majority of participants, that is 75% (N = 150), have done, at least, one prenatal consultation at a health center during their pregnancy. However, only 15% (N = 30) had received dietary advice and had no information about complications they could have during pregnancy or delivery and, therefore, did not have any special care for obese women.

Table 1 Sociodemographic characteristics and nutritional status of participants

Variable	Categories	Frequency	Percentage
Age (years)	18–25	56	28
	26–35	104	52
	36–43	40	20
Origin	Urban	97	48.5
	Rural	103	51.5
Educational level	Illiterate	88	44
	Primary	62	31
	Secondary	49	24.5
	Superior	1	0.5
Professional activity	Yes	8	4
	No	189	94.5
	Student	3	1.5
Health insurance	No	86	43
	Yes	114	57
Nutritional status	Moderate obesity	125	62.5
	Severe obesity	61	30.5
	Morbid obesity	14	7
Total	200		100

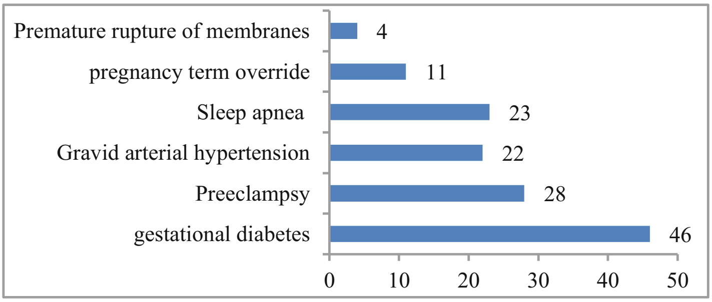

Fig. 1 Pregnancy-related complications

The majority of participants had complications during pregnancy (Fig. 1). Gestational diabetes occurred first with an incidence of 23% (N = 46), followed by preeclampsia at 14% (N = 28). In addition, 11.5% (N = 23) of pregnant women had sleep apnea and 11% had gestational hypertension. During child birth, caesarean delivery was the case for 38.67% (N = 78) of women and 10% had obstructed labor (Fig. 2).

Almost 33% (N = 66) of obese women had postpartum complications, the most common being infection (13%) and hemorrhage (12%) (Fig. 3).

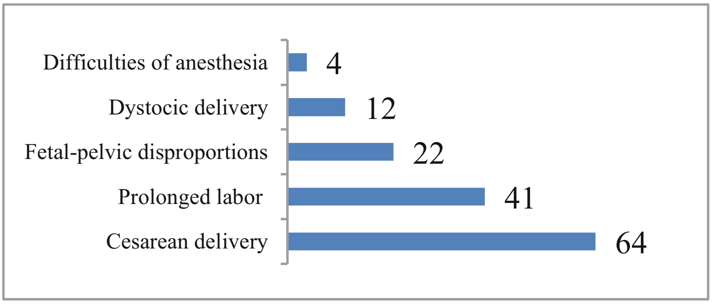

Fig. 2 Complications during delivery among participants

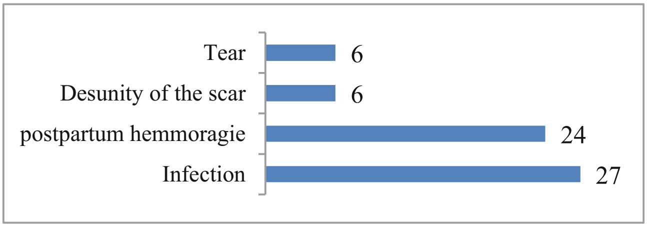

Fig. 3 Postpartum complications among participants

2.3 Discussion

Participants in this study are young, half of them of rural origin, have a very low level of instruction, without professional activity, and a modest economic level.

The majority of women presented with complications during pregnancy, the first being gestational diabetes. Indeed, gestational diabetes is one of the most common complications of pregnancy in obese women, which reflects a rise in maternal blood glucose that occurs during pregnancy from 26 weeks of age and disappears after childbirth. Obesity causes a decrease in insulin sensitivity, which is added to the phenomenon of physiological insulin resistance in pregnant women that develops during pregnancy and increasingly. It has been found that obese women are 2.6 times more likely to develop gestational diabetes (Marpeau et al. 2007; Deruelle 2011; Dolin et al 2018).

The rate of preeclampsy and gravid arterial hypertension was respectively 11% and 14% among participants. In fact, overweight and obese women are respectively 2.5 times and 4 times more likely to develop pregnancy-induced hypertension and has the serious complication of preeclampsy, leading to a high risk of eclampsy attacks that are responsible for maternal and perinatal mortality (Garbaciak et al. 1985; Deruelle 2011; Dod and Brilley 2017; Gregory et al 2018).

In addition, 11.5% (N = 23) of pregnant women had sleep apnea and 11% had gravid arterial hypertension. Sleep apnea syndrome and obesity have a well-established relationship. Overweight reduces thoracic wall compliance and increases respiratory tract resistance; these repeated periods of nocturnal desaturation have a role in the genesis of preeclampsia and in utero growth retardation (Mission et al. 2015; Dod and Brilley 2017; Dolin et al 2018).

Post-term delivery is also a consequence of obesity. According to the WHO definition, an outdated term is a pregnancy that extends beyond 41 weeks of completed amenorrhea. In fact, the duration of pregnancy increases in proportion to preconception BMI (Denison 2008; Deruelle 2011; Dod and Brilley 2017; Dolin and Kominiarek 2018). Similarly, it was showed an increased risk of post-term delivery by grade of obesity at 1.4, 1.5, and 1.8, respectively, for moderate, severe, and morbid obesity.

The cesarean delivery rate recorded in this study (38.67%) is well above the national average of 14% (MMH 2016). The increase in cesarean delivery and dystocic delivery in obese women has been reported by other authors (Djrolo et al 2002, Galtier et al. 2005 Deruelle 2011; Mission et al. 2015).

Postpartum in overweight and obese women is also a critical period where serious complications occur. In this study, 33% of women had postpartum complications; the most prevalent were infections and hemorrhages. Indeed, several studies have shown that the most common complication of postpartum in obese women is infection (endometritis, wall infections, cesarean, or episiotomy scar disruption) (Mission et al. 2015; Dod and Brilley 2017; Davis et al. 2018; Dolin et al 2018). Surgical-site infections are 2–3 times more frequent in overweight patients. These complications lead to a length of stay that increases proportionally with the BMI of patients, regardless of the mode of delivery (Galtier 2005). In addition, the risk of bleeding from delivery also increases with obesity (Mission et al. 2015; Dod and Brilley 2017; Davis et al. 2018; Dolin et al 2018). The incidence of other complications, such as pulmonary embolism and deep vein thrombosis, occurs, and also increases in obese women (Djrolo et al 2002; Galtier et al. 2005; Bringer 2008; Deruelle 2011).

2.4 Conclusion

In this study, we report a high incidence of complications in obese women during pregnancy, childbirth, and postpartum.

Dietary management of women of childbearing age is almost absent in Moroccan health-care facilities. Overall, the dietary approach should be integrated with the provision of care at all levels of the health system by scheduling preconception consultations, sensitizing women during pregnancy about complications of obesity, and the management of obesity cases. Also, prenatal consultations are very important for surveillance and early detection of a complication that can occur. These measures would reduce complications such as gestational diabetes, obstructed labor, and complications in the newborn.

3 Adhesion of Moroccan Women to the Mediterranean Diet Introduction

The effects of nutrition on human health have been widely demonstrated. Many chronic diseases could be prevented by a good dietary balance. The Mediterranean diet is a healthy diet that is characterized by the use of olive oil, as the main source of fat; the consumption of whole grains, especially wheat, starchy foods, vegetables, and fruits and fish; and little consumption of red meat (Panagiotakos et al. 2007; Martı´nez-Gonza´lez 2012; De la Montana 2012; Estruch et al. 2013). This diet is mainly adopted by the population around the Mediterranean sea.

The adoption of this diet is inversely related to the incidence of several pathologies. Indeed, this diet is known for its health benefits in general and its protection against cardiovascular disease. In addition, it is also known for its inverse association with obesity, overweight, metabolic syndrome, diabetes, and cancer (Panagiotakos et al. 2007; Martínez-Gonza'lez 2012; Montana 2012; Estruch et al. 2013; Schwingshackl et al. 2013; Schwingshackl and Hoffmann 2014; Echeverría 2017). Other studies have confirmed its positive association with better life expectancy (Knoops et al., 2004). It has also been reported the benefits of this diet in women during pregnancy by preventing allergies and asthma in newborns (Swell et al. 2013).

Several scores to assess the quality of diets among populations have been developed around the world. These are questionnaires on the frequency of food consumption based on the nutritional recommendations of each country. Some scores are intended for children and adolescents, for example, the Kidmed test developed in Spain (Montero 2006) and the ALES test (Index of Alimentação do Escolar) developed in Brazil (Molina et al. 2010). Other scores have been developed for adults in Greece (Panagiotakos et al. 2007), Chile (Echeverría 2017), and Spain (Martı'nez-Gonza'lez 2012).

In Morocco, a Mediterranean country, obesity and chronic diseases related mainly to eating behavior are increasing. In the context of the nutritional transition observed in developing countries, the authors aimed through this study to assess the adherence of Moroccan women to the Mediterranean diet using a Greek score (Panagiotakos et al. 2007) and to identify the associated factors.

3.1 Materials and Methods

Study Area It is a descriptive correlative cross-sectional study conducted in five selected primary health-care facilities in the region of Marrakech, three in the city center and two in the rural area.

Participants and Recruitment A sample of 1190 women was included in the study according to an accidental probabilistic sampling based on two major inclusion criteria:

– Women were of childbearing age.
– Women were able to answer the questions.

Data Collection Standardized interviews were used for data collection from eligible participants. The interview questions were tested among 10 women who were excluded from the main study sample. Information about women's sociodemographic characteristics, age, level of education, origin, marital status, and reproductive life, was collected. Weight and stature were measured to calculate the body mass index (BMI) of participants.

A Mediterranean diet score (MDS) was applied to participants to evaluate their adherence to the MD. In the absence of a Moroccan MDS, the authors opted for the score developed in Greece from the ATTICA study (Panagiottakos et al. 2007). It is a score that includes 11 food groups close to Moroccan food habits: unrefined cereals, potatoes, fruits, vegetables, fish, red meats and derivatives, poultry, whole dairy products, and the use of olive oil in cooking (Panagiottakos et al. 2007). Evaluation of a number of shares consumed per month (from 0 to 18) of the following food groups: unrefined cereals, potatoes, fruits, vegetables, fish, red meats and derivatives, poultry, and whole dairy products. The use of olive oil in cooking is evaluated from ever (0) to daily use (5). The consumption of alcoholic beverages is evaluated, on the inverse scale, by the quantity consumed per day (in ml) (Table 2). For consumption of food presumed to be close to this diet, a score ranging from 0 (no consumption) to 5 (more than 18 parts/month) is assigned. For the consumption of presumed foods far from this diet, one attributes scores with an inverse scale. Subsequently, the sum of the scores allocated to each food group is calculated and ranges from 0 to 55 (Table 2).

Ethical Considerations Before starting the study, the authors received approval from the local ethics committee of the Ministry of Health. All participants were informed by the objective of the study and gave their free informed consent to participate in the study.

Data Analysis The authors used the SPSS Logiciel (version 10) for data analysis. To describe participants' characteristics, means and standard deviations were calculated for the quantitative variables while frequencies and percentages were done for the qualitative variables. Women's body mass index was calculated according to BMI = weight(kg)/size^2 (m). Also, univariate regression was applied to variables to determine the associated factors to the MD adherence.

Table 2 The Mediterranean diet score

	Frequency of consumption (servings/month)					
How often do you consume	*Never*	*1—4*	*5—8*	*9—12*	*13—18*	*>18*
Non-refined cereals (whole grain bread, pasta, rice, etc.)	0	1	2	3	4	5
Potatoes	0	1	2	3	4	5
Fruits	0	1	2	3	4	5
Vegetables	0	1	2	3	4	5
Legumes	0	1	2	3	4	5
Fish	0	1	2	3	4	5
Red meat and products	5	4	3	2	1	0
Poultry	5	4	3	2	1	0
Full fat dairy products (cheese, yoghurt, and milk)	5	4	3	2	1	0
Use of olive oil in cooking (times/week)	*Never*	*Rare*	*< 1*	*1—3*	*3—5*	*Daily*
	0	1	2	3	4	5
Alcoholic beverages (ml/day, 100 ml = 12 g ethanol)	*<300*	*300*	*400*	*500*	*600*	*>700 or 0*
	5	4	3	2	1	0

Source: Panagiotakos et al. (2007)

3.2 Results

Table 3 represents the sociodemographic characteristics of our study population. Participants ranged from 15 to 49 years, with the group age average being 28.43 years (SD: 7.49). In total, 752 (63.1%) women were from urban origin. More than 76% of women were married, more than 50% were illiterate or have just been in primary school, and more than 83% were housewives. More than 50% of women did not have health insurance.

3.3 Characteristics of Women's Reproductive Life

At the moment of study, 30.7% (N=304) of participants were pregnant and 24.6% were breastfeeding. The mean age at puberty among participants was 13.05 years (SD=1.54) while the mean age at first marriage (N=764) was 21.14 years (SD=3.83). The first pregnancy occurred on average at 22.64 years (SD=4.33), and the average parity (N=583) was 2.09 (SD=1.33).

Table 3 Sociodemographic characteristics of participants

Variable	Category	Count	Percentage
Age (N=1190)	15–25 years	503	42.3
	26–35 years	446	37.5
	36–49 years	241	20.3
Origin (N=1190)	Urban	752	63.1
	Rural	439	36.9
Marital status (N= 986)	Married	750	76.1
	Divorced	28	2.8
	widowed	17	1.7
	Single	191	19.4
Level of education (N=1190)	Illiterate	290	24.4
	Primary	340	28.6
	Secondary	370	31.1
	Superior	190	16
Professional activity (N=1190)	Yes	191	16.1
	No	987	83.1
	Student	10	0.8
Health insurance (N=1189)	No	645	54.2
	Yes	544	45.8

Table 4 Participants' nutritional status

Nutritional status	Frequency	Percentage
Thinness	14	1.4
Normal	403	41.2
Overweight	366	37.5
Obesity	194	19
Total	977	100

3.4 Nutritional Status of Participants

The analysis of the body mass index involved 977 women. There is an overweight rate of 37.5% and a rate of obesity of 19% (Table 4).

3.5 Physical Activity Among Participants

Among 1186 women, only 39% (N = 463) reported practicing a physical activity (30 minutes walking or equivalent) while 60.7% (N = 723) were sedentary. Physical activity ranges from 1 to 7 times/week with an average of 1.7 times/week (SD = 1.45).

3.6 Women's Adherence to the Mediterranean Diet

The data of the Mediterranean diet score (MDS) included 741 women. The score ranges from 22 to 50 with an average of 35.96 (SD = 4.4). Based on the average score of the MD obtained, we subdivided our population into two groups: a first group characterized by a low to medium adhesion to MD (MDS ranged from 0 to 35), which represents 58%, and a second group characterized by a good to very good adhesion to MD (MDS ranged from 36 to 55), which presented 42%.

The correlation between MD score and sociodemographic characteristics of women showed a very high statistical significance ($P<0.001$) with level of education, professional activity, and health insurance. Indeed, women with a good level of education, with a professional activity, and a good health insurance were more likely to adhere to the Mediterranean diet than others. Also, the association between nutritional status showed a significant association. Thus, overweight and obese women are the least adherent to MD ($P=0.003$).

On the other hand, women's age, origin, and matrimonial status did not have any effect on the adherence to the MD (Table 5).

3.7 Discussion

In this study, overweight and obesity among women were above the national average of 2016 (Moroccan Ministry of Health (MMH), 2016). Similar results have been found in other regions of Morocco (Aboussalah and Sbaibi, 2015). The majority of participants did not practice any physical activity.

The correlation between MD score and nutritional status showed a significant association. Thus, overweight and obese women had the lowest MD scores. The same results have been reported by other studies (DelaMontana et al 2012; Martínez-Gonza'lez 2012; Echeverría et al. 2017). The adherence to MD is variable among women. Indeed, some factors increase the adherence, such as level of education, health insurance such as CNOPS, CNSS, and professional activity. The health insurance is an indicator of a stable economic situation and well-being of the person (CNOPS and CNSS are insurance for functionary and salaried persons while RAMED is insurance for the poor population without a regular work). Indeed, a good socioeconomic level would be a favorable factor of the quality of food consumed (fish, use of olive oil, fruit, whole grains, etc.) and allows preparation of dishes respecting the nutritional balance. Also, women who reached an advanced level of education would be more sensitized and have knowledge about the nutrition that affects their food choices (Yahia et al. 2016), which explains their better MD scores.

Table 5 Association between participants' characteristics and MD adherence

Variable	Categories	0<MDS<=35 N(%)	35<MDS<=55 N(%)	Chi-carré	P value
Age	15–25 years	194 (59%)	135(41%)	2.381	0.304
	26–35 years	136 (54.4%)	114(45.6%)		
	36–49 years	100 (61.7%)	62(38.3%)		
Origin	Urban	293 (57%)	221(43%)	0.725	0.22
	Rural	137 (60.4%)	90(39.6%)		
Matrimonial status	Married	303 (56.5%)	233(43.5%)	6.35	0.09
	Divorced	6 (50%)	6(50%)		
	widowed	10 (99.1%)	1(0.9%)		
	Single	111 (61%)	71(39%)		
	Illiterate	119 (78.3%)	33(21.7%)	47.15	0.00[b]
	Primary	131 (63.3%)	76(36.7%)		
Educational level	Secondary	114 (45.8%)	135(54.2%)		
	Superior	66 (49.6%)	67(50.4%)		
Professional activity	Yes	61 (45.2%)	74(60.9%)	11.18	0.001[b]
	No	369 (44. 8%)	237(39.1%)		
Health insurance	No	279 (65.3%)	148(34.7%)	29.32	0.00[b]
	RAMED	60 (59.4%)	41(40.6%)		
	Others	91 (42.9%)	121(57.1%)		
Nutritional status	Thinness	5 (41.7%)	7(58.3%)	14.32	0.003[a]
	Normal	169 (51.8%)	157(48.2%)		
	Overweight	156 (61.2%)	99(38.8%)		
	Obesity	96 (68.1%)	45(31.9%)		

MDS, Mediterranean diet score
[a] Moderate statistical significance
[b] High statistical significance

3.8 Conclusion

Through this study, we highlight the increase in overweight and obesity rates among participants, lack of physical activity, and an insufficient adherence to MD. This observation raises the importance of nutrition education for the general population and women in particular. In addition, it is important to operatioanalize the Moroccan guide of nutrition (MS, 2016) and to adapt it to the Moroccan nutritional habits as wel as to the purchasing power of the citizen.

4 Infertility and Nutrition Introduction

Worldwide, infertility is a public problem during the reproductive age affecting about 10–15% of couples attempting to achieve pregnancy. Infertility is defined as the inability to conceive a child after 12 months of conception testing with regular sexual intercourse (World Health Organization (WHO) 2002). The origin of infertility may be due to the man, the woman, or both. Among the causes of the alteration of certain parameters of reproductive health, we emphasize genetic or constitutional causes, first the behavioral dimension (later procreation, especially for women and smoking), overweight, obesity, and environmental exposures (INSERM 2012).

The most common causes in women are polycystic syndrome and cycle disorder (Lash et al. 2008). In addition, according to many studies, overweight and obesity are responsible of several idiopathic infertility cases (Donnadieu et al. 2009).

This study focuses on nutrition and infertility. It aims to describe the socioeconomic characteristics of infertile women, their nutritional status, and eating habits since nutrition is a determinant of fertility according to several research studies.

4.1 Materials and Methods

Study Area This cross-sectional quantitative descriptive study was conducted in 2015 in Marrakech city. Data were collected at the gynecological consultation at the University Hospital Center Mohamed VI (CHU, MVI) in Marrakesh, Morocco.

Population A sample of 100 infertile women was included in the study according to an accidental probabilistic sampling.

Data Collection Standardized interviews were used for data collection from eligible participants. We collected information about women's sociodemographic status. Weight, stature, and waist circumference of participants were measured to calculate the body mass index (BMI) and evaluate abdominal fat.

Ethical Considerations Before starting our study, we received approval from the local ethics committee of the Ministry of Health. All participants were informed of the objective of the study and gave their free informed consent to participate in the study.

Data Analysis Data were analyzed by the SPSS software (version 10). We calculated the means and standard deviations for the quantitative variables and the frequencies and percentages for the qualitative variables.

Women's body mass index was calculated according to BMI = weight(kg)/size^2 (m)

5 Results

Sociodemographic characteristics of participants are represented in Table 6. The age of participants ranged from 19 years to 53 years, and the average age is 30.77 years (SD=5.3). Also, 78% were below 35 years of age and 67% were of urban origin. More than 63% of participants had reached a secondary or superior level of education. However, only 16% had a professional activity.

5.1 Reproductive Life and Infertility

Among participants, 45 % had a duration of marriage more than five years and 87% declared having regular unprotected sexual intercourse. The cause of infertility was diagnosed as 58% women while 42% of infertility cases were idiopathic. Polycystic syndrome was the leading cause of known infertility (41.4%) (Table 7).

5.2 Nutritional Status of Participants

The analysis of women's body mass index showed more than 54% of excess weight including 31% overweight, 15% moderate obesity, and 8% severe obesity. Also, 46% of women had a waist circumference more than 88 cm. In parallel, we noted a lack of physical activity for more than 74% of participants.

Table 6 Sociodemographic characteristics of participants

Variable	Categories	Frequency	Percentage
Age (years) (N=100)	18–35	78	78
	>35 years	22	22
Origin (N=94)	Urban	63	67
	Rural	31	33
	Illiterate	17	17
Educational level (N=100)	Primary	20	20
	Secondary	38	38
	Superior	25	25
Professional activity (N=100)	Yes	16	16
	No	68	68

Table 7 Reproductive and infertility characteristics of participants

Variable	Categories	Frequency	Percentage
Duration of marriage (N=100)	< 5 years	55	55
	>5 years	45	45
Regular unprotected sexual Intercourse (N=100)	Yes	87	87
	No	13	13
Cause of infertility diagnosed (N=100)	Yes	58	58
	No	42	42
Diagnosed causes of infertility (N=58)	Polycystic ovary syndrome	24	41.4
	Uterine malformation	8	13.8
	Cycle disorder	6	10.3
	Endometriosis/pelvic adhesion	7	12.1
	Other causes	13	22.4

5.3 Discussion

Participants were mostly of urban origin and had a good level of education; however, 84% were housewives. The majority did not have any physical activity. The rate of overweight and obesity exceeded 54%. Overweight is a known factor of infertility. Indeed, the risk of anovulation is multiplied by 1.3 for a BMI between 24 and 25.9 kg/m^2 and by 3.7 for a BMI greater than 32 kg/m^2 . The risk of over one year to conceive is increased by 27% in the case of overweight in the women and 78% in the case of obesity. In addition, a BMI greater than 25 kg/m^2 is also associated with a 67% increase in the risk of early spontaneous abortion (SCF) and also repeated FCS (Pesant et al. 2010).

The polycystic syndrome (PCOS), a major cause of infertility, is related to overweight and fat distribution around the waist. There is a link between BMI and fertility in this pathology, in addition to insulin resistance, frequently associated with PCOS, which increases the production of androgens and testosterone that directly inhibits ovulation; moreover, it recommends weight loss to improve fertility (INSERM 2012). In parallel, we noted a lack of physical exercise for more than 74% of the women in the study. Similarly, Pesant (2010) concedes that a woman's weight loss also improves the metabolic profile, ovulatory regularity, and the chances of uncomplicated pregnancies, and asserts that physical exercise helps to maintain the loss of weight and improves insulin sensitivity even without weight loss.

Results showed that over 70% of women have a waist circumference of between 80 and 88 cm, and 45.7% greater than 88 cm in the category of abdominal obesity. It is known that the distribution of fat at the abdominal level is directly related to the prevalence of disorders of the cycle. Abdominal obesity causes hyperandrogenism and predisposes to PCOS (Pesant 2010).

5.4 Conclusion

Therefore, overweight and abdominal obesity in some women among the study participants may be responsible for infertility, especially as 42% of infertile couples studied have no cause of diagnosed infertility. Indeed, there is no dietary care for these women.

In perspective, the authors intend on studying the correlation between nutritional status and infertility to evaluate the association between them and to sensitize health responsible to propose specific care to overweight infertile women. More in-depth investigations in this line of research are possible.

6 General Conclusion

The emerging nutritional disorders are related to urbanization, changes in lifestyles and nutrition, and have many health and economic consequences. Therefore, it create new challenges for the national health system. More efforts are required to develop a comprehensive nutritional policy integrating the Moroccan culture and the sociodemographic conditions of citizens. Also, the dietary approach should be integrated into the health-care system, especially among women of childbearing age.

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Effects of Mercury on General Homeostasis and Liver–Brain Interaction

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Abstract Contamination of food with mercury is a real health issue for humans with physiological consequences with harmful effects on living organisms. The danger of the metal became more effective during the last century due to its extensive use. According to previous studies, the metal has been found in the hair since the fifteenth century and its rate has tripled in the twentieth century. Its toxicity has been demonstrated dramatically in highly contaminated areas such as Minamata Bay, Japan, in the 1950s and 1960s. Permitted mercury levels are a real controversy. Knowing mercury toxicity, the question is, what is the safe level of exposure? If low doses of mercury have been fixed by legal authorities and agencies to be not harmful for health, rare studies have addressed the potential effects of low doses, taken chronically, on health. In this chapter, we review the effect of nonessential heavy metals and principally mercury (organic and inorganic forms) on general physiology. It is noteworthy that the liver is the first principal target of all xenobiotics including heavy metals. The metabolites of these heavy metals could then reach kidney, brain, as well as other organs and exert their effect locally.

Keywords Food · Heavy metals · Mercury toxicity · Health · Liver · Kidney · Brain · Exposure · General physiology

1 Introduction

Mercury is a heavy metal widely used in metallurgical activities since antiquity and rediscovered at the time of the industrial revolution. Mercury is a silvery-white metal, shiny, very dense, and very mobile. It is the only liquid metal at room temperature, which earned it its symbol (Hg) from the Latinized Greek word hydrargyrum (liquid silver). Elemental mercury or metal mercury is volatile at usual ambient temperatures (enough to cause intoxication) and is practically

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insoluble in water. It forms amalgams with many metals. In addition to the element itself (HgO), mercury can exist in two main valences +1 and +2, corresponding to the mercury and mercuric compounds. The speciation affects significantly the kinetics and the toxicity of mercury, which is a cumulative toxic.

2 Mercury and Health

The effects of exposure to this metal on health depend on the chemical form in which the element is found (elementary, inorganic, or organic), the route of exposure (inhalation, ingestion, or skin contact), and the level of exposure itself (the concentration at which the metal has been given). Thus, liquid elemental mercury vapors as well as methylmercury display high absorption compared to inorganic mercury salts and can therefore be more harmful. Consequently, it is important to reduce exposure to all forms of mercury as much as possible.

As any other xenobiotic, the metal mainly enters the body through the digestive and pulmonary routes, although the first route represents the essential way of contamination. It is first transported by the blood where it can be dosed. It accumulates mainly in the liver, kidneys, lungs, and brain (Agarwal et al. 2007). It alters the biology of the cell by disrupting many metabolic pathways and different physiological processes. Some studies suggest that mercury, even at low levels, could exert a deleterious effect on brain (Uversky et al. 2001; Olivieri et al. 2002), kidney (Hua 1993), and hepatic function (Carmichael & Fowler 1979; Al-Saleh et al. 2005; Necib et al. 2013)

During these two decades, toxicological research has focused on the induction of oxidative stress (SO) after exposure to heavy metals as a possible mechanism of toxicity. Following several studies, heavy metals including mercury, with such properties, have been shown to cause the overproduction of reactive oxygenated species (ROS) in the intra- and extracellular spaces (Gassner et al. 1997; Barja 1999), resulting in disturbance of cell prooxidant/antioxidant balance which can induce to create an oxidative stress state.

3 Environmental Source of Exposure

The environment represents the main source of contamination with this metal. It is mainly represented by the consumption of contaminated foodstuffs, by the natural degassing of the Earth's crust, the latter discharging several tons of mercury annually, and by volcanic activity. Regarding exposure by ingestion of contaminated foodstuffs, it should be remembered that the transformation of mineral mercury into methylmercury takes place in the sediments of rivers, the ocean, and other aquatic grounds; so it's mainly the fish that's at fault. Indeed, anaerobic conditions existing in water, and inorganic mercury is transformed into methylmercury by the action of microorganisms, which is then absorbed by plankton, itself ingested by fish.

Methylmercury, therefore, accumulates in aquatic organisms, which we will then consume. We must remember the “Minamata Disease” or severe mercury poisoning of many fishermen from Minamata Bay in Japan, following the consumption of fish contaminated with mercury by the spill in the bay, between 1953 and 1956, plant waste (producing vinyl chloride and using mercury chloride and sulfate as catalysts) (Watts J et al. 2001). The episode of the poisoning of soldiers in Iraq (1956, 1960, and 1972), Pakistan (1961), and Guatemala (1963, 1964, and 1965) by eating bread made with contaminated grains and freshly treated with organomercurials is also another clear example concerning the negative sides of the metal on the health (Brent 2001). We must notice that agriculture uses mercury for the preparation of fungicide, insecticide, and bactericide for the manufacture of fertilizers and conservation of seeds. The nonrespect of good practices when using these phytochemical products during treatment could lead to serious problems.

4 Food

By consumption of fish, on average from 2 to 20 μg/day with interindividual variations, mercury has the capacity to accumulate in organisms (bioaccumulation) and to concentrate throughout the food chains (bioamplification), particularly in the aquatic food chain, fish (especially trout, pike, and perch fresh), and predatory marine mammals (sharks, large tuna, and swordfish in seawater) (Clarkson T et al. 1998; United Nation 2002). The higher a fish is in the food chain, the more it tends to have a high level of mercury. This could be added to metal trace in other food matrices, notably, vegetables treated by phytocompounds containing inorganic mercury but also meat derivatives and dairy products obtained from animals nourished by treated vegetables as cited above (Clarkson T et al. 1998).

5 Absorption Mercury Derivatives

For organic mercury, digestive absorption is majorly due to its high lipid solubility (for the general population, it is the most frequent mode of contamination because exposure is from food) (Givica-Perez et al. 2001).

6 Distribution and Metabolism

At the plasma level, mercury, whatever its chemical form, is distributed between red cells and plasma proteins, but in different proportions.

The binding to plasma proteins of metal mercury is 30% against 75% for mercuric salts. Organic derivatives preferentially bind to red cells. The elementary mercury Hg is oxidized by a catalase into the mercuric ion Hg^2 +, and the strong affinity of the latter for the thiol SH groups of proteins means that it is not very diffusible because it is largely linked to cellular or blood proteins.

The rapid distribution mainly concerns the kidneys (80% of the body burden) and in smaller quantities the liver and the brain, and note that inorganic derivatives accumulate very little in the brain compared to other forms of mercury (the monovalent salts being those that accumulate there least).

The liver represents the main organ target when the metal is metabolized independently to its chemical form. Once it arrives, it is bio-metabolized by a multitude of enzymes to be transformed into another chemical form to decrease its harmful effects and also to increase its ability to be conjugated with endogenous components to be then easily excreted and eliminated in the feces or in the urine by renal excretion. Then, only the remained part reaches other organs in the body. This retained part by the organism has a significantly increased half-life (Smith 1994).

7 Elimination

It is done by renal and fecal route in different proportions depending on the chemical form of mercury.

Mercury metal is eliminated in the urine as much as in the stool.

- The excretion of organic mercury is 90% fecal (predominant digestive contamination). After its excretion in the bile following its hepatic biotransformation, the obtained compound enters the small intestine and either reabsorbed into the gut (liver–bile–small intestine–reabsorbed into blood–back to liver) or excreted through feces) (Smith 1994).
- The renal part excreted of inorganic mercury is discreetly higher than the fecal part. It should be noted that in acute accidents, a fraction of about 7% is eliminated by the pulmonary route.

The elimination of the nonaccumulated fraction of metal mercury is slow (biological half-life of 6–10 weeks). According to a compartmental pharmacokinetic model, the half-life of methylmercury in the body is 44 days (Smith 1994).

The maximum amount of mercury spontaneously eliminated daily by the body, all chemical forms combined, is 20 μg/day.

8 Mechanisms of Action

8.1 Mercury Has Cytotoxic Activity

On the one hand, the affinity of Hg^{2+} ions for thiol SH groups leads to the blocking of thiol functions of proteins (thus modifying their tertiary and quaternary structure), peptides (glutathione), or sulfur amino acids (cysteine) (INERIS 2010). The inactivated proteins can be enzymes (thiol-dependent enzymes at the level of lysosomes and mitochondria), membrane proteins of cellular organelles, membrane proteins involved in ion transport (ATPase Na-K, calcium channels), or tubulin and myelin, which causes serious disturbances in the conduction of nerve impulses. On the other hand, mercury inhibits cellular protection systems against free radicals. Mercury also causes lysis of cell membranes; no doubt by catalyzing the oxidation of a particular membrane phospholipid, mercury also inhibits zinc enzymes due to competition between these two metals (same column in the classification table elements).

8.2 Mercury Has Genotoxic Activity

Upon its arrival in the cell, the metal enters the nucleus and could act at the genomic level. Mercury disrupts DNA synthesis, and in the form of a divalent cation (Hg^{++}), it has a mutagenic action and aggravates the genotoxic effects of ionizing radiation by inhibiting DNA repair mechanisms in cells.

The clastogenic effects of mercury (chromosome breakage, presence of fragments or supernumerary chromosomes, absence of centromere) have been observed in lymphocytes of subjects who ingested fish contaminated with methylmercury (Silvio et al. 1994).

8.3 Mercury Has Dysimmune Activity

Mercury (Hg) has been shown to induce renal autoimmunity due to nephritis induced by an autoantibody (auto-Ab), which is dependent on the major histocompatibility complex (MHC) haplotype (Henry et al. 1988; Hultman and Eneström 1988; Hultman et al. 1993). Different forms of Hg, for example, methyl Hg (MeHg), ethyl Hg, and inorganic Hg (Hg2 +) differentially affect immunity (Havarinasab and Hultman 2005).

9 Chronic Toxicity

In humans, the two main target organs for elemental mercury and inorganic mercury are the central nervous system and the kidney. Thus, the main symptoms of chronic hydrargyrism (mercury poisoning) are neurological such as psychomotor disorders, cognitive disorders, and personality changes (such as irritability and anxiety). Mercury also reaches the kidneys (glomerular and tubular lesions) and induces proteinuria (Jung-Duck and Wei 2012). Finally, cardiovascular (tachycardia, hypertension), respiratory, hepatic, and immunological disorders are also observed. Organic mercury mainly reaches the brain, with paraesthesia, general malaise, changes, and sensory disturbances. Methylmercury induces Minamata disease with the onset of severe neurological disorders. Organic mercury also causes kidney damage. The same observations are made in animals, and the target organs are the same (INERIS 2010).

9.1 Effects on the Digestive Tract

Mercury is absorbed by cell epithelial once it is consumed. The absorbed mercury can lead to various digestive problems as it can stop the digestive enzymes production such as chymotrypsin, pepsin, and trypsin, as well as the function of dipeptyl peptidase and xanthine oxidase (Vojdani et al. 2003). The activity of mercury on the gastrointestinal system commonly presents as indigestion bloody diarrhea abdominal pain, ulcers, inflammatory, and bowel disease. Mercury ingestion has additionally been linked with the dysregulation of the intestinal flora, causing an increase in the quantity of nondigested food in the bloodstream, leading to immune decreasing and pathogenic infections resistance (Summers et al. 1993).

9.2 The Effect of Mercury on the Liver

The liver is the organ that participates in the distribution, detoxification, and transformation of contaminants, and constitutes in that the choice target of inorganic mercury (Havelková et al. 2008). Indeed, data obtained from previous investigations in the laboratory have demonstrated that inorganic mercury causes hepatotoxicity in adult mice, although treated by low HgCl2 doses (5 mg/kg) with elevation in serum alanine (ALT) and aspartate (AST) aminotransferase activities known as the markers of hepatocellular damage (Kumar et al. 2005).

Liver cytolysis is a sign of acute mercury poisoning (Necib et al. 2013). It is only observed after massive contamination. Mercury inhibits the synthesis of hemoproteins, and in particular that of cytochrome P450, which can cause drug interactions and the toxic effects of other substances (Amara I et al. 2014).

Although these negative manifestations have been well characterized, the involved mechanisms are not fully known. In zebrafish model, it has been shown that the analysis of transcriptome showed that premature targets of mercury caused toxicity of the liver linked with nuclear receptor signaling, mitochondrial processes, and apoptotic signaling pathway (Ung et al. 2010). Furthermore, after 24 h treatment with inorganic mercury, it increases expression of proteasome signaling pathway and system complement has also been shown, suggesting elevation of degradation of damaged proteins and activation of acute-phase response.

In experimental conditions with 96 h treatment, the authors reported that numerous critical routes linked with the cellular process, metabolism, survival, and stress were noticeably deregulated in the hepatic system. Concerning the effects of the organic mercury (Gonzalez and Using 2005), a similar model, that is, zebrafish shows that the involved genes in DNA repair, apoptosis, detoxification process, and mitochondrial metabolism were commonly deregulated. Interestingly, proteasome pathway and DNA damage were upregulated in HepG2 cells and zebrafish liver. Furthermore, electron transport chain, mitochondrial fatty acid beta-oxidation, and nuclear receptor signaling pathway were decreased by HgCl2 in human HepG2 cells and zebrafish liver, showing similar mode of action (Ung et al. 2010). The observed biological effects concerning the signaling pathways in zebrafish liver could explain the modifications in cytoskeletal proteins, cell adhesion, cell morphology, and the decrease of hepatic parenchyma cell number (via intrinsic apoptotic induction) showed in HgCl2-treated zebrafish liver. In another more recent study in liver zebrafish, the authors have described vacuolization of cytoplasm, reduction in glycogen granules and lipid droplets, increase of pyknotic nuclei, rough endoplasmic, and reticulum number of mitochondria. The observed effects are concomitant to the induction of metallothionein (MT) as protection from the toxic effects generated by the metal (oxidation, denaturation, and misfolding of protein) (R. Macirella et al. 2016).

Mercury undertakes high biliary hepatic cycling when it is released into bile, but it is moderately resorbed in the portal circulation to reach hepatic system. In the bile, the conjugated form of mercury with glutathione is transformed into mercury L-cysteine complex before reaching the circulatory system.

9.3 The Effect of Mercury on the Kidneys

The ionized mercury Hg^{2+} will accumulate in the proximal tubules of the kidney and the superficial area of the external medulla. The inorganic form, like mercury chloride, is known as a nephrotoxic agent (Emanuelli et al. 1996; Clarkson 1997) and causes renal insufficiency. During high exposures to elemental or inorganic mercury, dose- dependent tubulopathies and glomerulonephritis with extramembranous deposits of immunotoxic mechanism are observed (Hua 1993). Tubular damage seems to occur beyond a certain exposure threshold, conventionally when the urinary excretion of Hg exceeds 50 μg/g of creatinine (Testud 2005).

Mercury may also lead to kidney damage, and the data proposes an association between exposition of mercury and nephrotic syndrome, chronic renal failure kidney, cancer, and acute tubular necrosis (Tchounwou et al. 2003; Li and et al. 2010).

Other studies have shown that exposure to mercury can lead to various kidney damages, including nephrotic syndrome by subacute poisoning, tubular dysfunction, secondary segmental glomerulosclerosis, glomerular disease, proteinuria, and glomerulonephritis membranous (Miller et al. 2013). Thus, it has been reported that the metal could reduce the function of tight junction protein in kidney and disturbs cellular permeability. It decreases transepithelial electrical resistance (TER) and facilitates the phosphorylation of tight junction protein, occluding, via a protein kinase A (PKA)-dependent mechanism (Kawedia et al. 2008). These harmful effects have been described as a result of free radical generation (myeloperoxidase activity and MDA), and protein urea (activities of N-acetyl-beta-D-glucosaminidase (NAG) (Otal et al. 2018). The absence or the reduced amount of detoxifying protein or those with antioxidant activity (Branco et al. 2012; Wang et al. 2014; V) also promotes the negative effects of the metal, causing the proximal tubule damage and the sensitivity of lysosome could also be attributed to proteinuria (Reyes et al. 2013). Physiological conditions could influence the amount of the metal in the kidney and its local actions. Thus, the amount of mercury in blood and total renal mass has been reported to be significantly lower in pregnant rats than in nonpregnant rats. This has been explained to be due to the expansion of plasma volume in pregnant rats and dilution of mercury, leading to lower levels of the metal in maternal blood and kidneys (Orr et al. 2018). On the other hand, a previous study revealed that females are more vulnerable to kidney toxicity exposed to Hg and effect on pars recta tubule cells are assumed to contribute to proteinuria (Wang et al. 2014).

We have to note that the renal tissue and function remain highly sensitive to inorganic mercury effects as in an experiment, researchers showed that even 21 days after the end of mercury exposure rats presented an increase in serum creatinine and urea levels of 278% and 240%, respectively (Franciscato et al. 2011). The authors showed also that pretreatment with zinc alleviated this effect partially; indeed, zinc has been previously categorized as preventive against mercury-induced general toxicity and notably nephrotoxicity. Similar results about renal toxicity and zinc preventive action were also obtained when animals were euthanized 24 h after the end of mercury exposure (Peixoto et al. 2007). Interestingly, it has been found that mercury-treated animals still presented an increase of mercury content in kidney tissues 21 days after the arrest of treatment (Franciscato et al. 2011). This has been explained as an attempt of the organism to eliminate the metal that bound easily to many endogenous components like metallothionein (metallothionein–Hg); (Peixoto et al. 2007), glutathione (glutathione–Hg), and cysteine (cysteine–Hg–cysteine), thiols that are easily taken up by kidney, causing accumulation of the metal in this organ (Zalups 2000).

9.4 Effects on Cardiovascular System

Mercury has also been proposed to act negatively on cardiovascular system affecting that regulatory system. For example, in a sample of persons consuming contaminated fish, it was showed that exposition to mercury with frequent consumption of this kind of fish is susceptible to lead to an increase in arterial blood pressure (Halbach 1990) and to myocardial infarction as well as to coronary dysfunction and atherosclerosis (Rhee et al. 1989; Guallar et al. 2002). Concerning this latter manifestation, it has been reported that mercury concentrations are predictors of the oxidized low-density lipoprotein (LDL) levels (K. Yoshizawa et al. 2002). Indeed, oxidized LDL molecules are commonly showed in atherosclerotic lesions and are linked to atherosclerotic disease (Salonen et al. 1995; Houston et al. 2007) and acute coronary insufficiency (Virtanen et al. 2005). Also, mercury exerts toxicity on the cardiovascular system passes via the suppression of the "paraoxonase" (J. Hulthe and B. Fagerberg, 2002), an enzyme that decreases the oxidation of LDL and that has a significant antiatherosclerotic effect (Halbach 1990). The harmful effects of the metal seemed to pass via the generation of free radicals during oxidative stress and a decrease in the effect of antioxidant enzymes (like glutathione peroxidase) (Ehara et al. 2001; Mackness and Mackness 2004). This leads to a drastic reduction in glutathione and selenium playing a crucial role in antioxidant effects. On the other hand, treatment with mercury has been shown to produce a negative inotropic activity in perfused hearts. The decrease in contractility was clarified with the changes in protein expression of SERCA, calcium-handling mechanisms; Na+ K+ ATPase (NKA), and sodium/calcium exchanger (NCX) was reduced; increase of phospholamban expression; and β-adrenergic stimulation response was diminished after mercury exposition (Massaroni et al. 1992; Furieri et al. 2011).

10 Effects of Mercury on Reproduction

Mercury can lead to pathophysiological fluctuations along the gonadal and hypothalamus–pituitary–adrenal axes that can have an impact on the reproductive system by altering follicle-stimulating hormone (FSH) circulation, level of luteinizing hormone, and inhibition of progesterone and estrogen (Davis et al. 2001; Schrag et al. 1985). It decreases fertility after exposition to mercury in the workplace (Rowland et al. 1994; Colquitt 1995).

A Hong Kong study showed that high amounts of mercury are linked with infertility in men (Dickman et al. 1998). Also, mercury can have adverse effects on spermatogenesis (Boujbiha et al. 2009), the number of epididymal spermatozoa, and the weight of the testes. There is also evidence that links mercury with erectile dysfunction (Schrag et al. 1985). Additionally, mercury has been linked with the inhibition of LH and FSH, which affect the progesterone and estrogen levels, leading to an inclined uterus, irregular periods, premature menopause, or painful and ovarian dysfunction (Chen et al. 2006). There is strong evidence associating mercury with menstrual dysfunction, including painful periods, abnormal bleeding, and irregular cycles (Davis et al. 2001).

11 Effect of Mercury on Nervous System

Low-dose mercury affects adults' neuronal system. Small amounts of certain metals, such as mercury, can directly lead to induce alpha-synuclein fibril formation, constituting the main intracellular protein inclusions (Lewy bodies and Lewy neurites) in dopamine neurons of the substantia nigra, leading to Parkinson's disease (Uversky et al. 2001).

In addition, low concentrations of cobalt and mercury can induce oxidative stress, cellular cytotoxicity, and increase the secretion of ß-amyloid 1-40 and 1-42, which can lead to neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Olivieri et al. 2002). Mercury binds to sulfhydryl groups in proteins and disulfide groups in amino acids, which blocks related enzymes and inactivates sulfur (Mathieson 1995; Markovich and James 1999). In addition, it modifies the membrane cell's permeability through binding to the sulfhydryl radicals (Bapu et al. 1994).

11.1 Mercury and Oxidative Stress

Many previous studies have reported that mercury given at high doses could lead to lipid peroxidation. Recently, the work of Malqui et al. (2018) has shown that this peroxidation could occur also at low mercury levels given continuously. In any case, this effect of the metal could not be a direct one as Seppänen et al. (2004) reported that mercury does not promote the direct nonenzymatic peroxidation of low-density lipoprotein (LDL) for example. They showed firstly that mercury and methylmercury do not promote direct lipid peroxidation, but that, secondly, a simultaneous exposure to high inorganic mercury, copper, iron, and low selenium concentrations can lead to a condition in which mercury promotes lipid peroxidations. They also explain that this mechanism gives a reasonable molecular-level clarification for the showed relationship between atherosclerosis and high body mercury content.

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Prostate Cancer Incidence and the Consumable Risk Factor Effect in the Metropolitan City of Ibadan

Abiola Oduwaiye, Godwin Ikwuyatum, Ayobami Popoola, and Femi Oni

Abstract The incidence of cancer is an emerging public health problem in Nigeria. Using secondary data from the University College Hospital Ibadan from 1993 to 2012, the study investigated the spatial–temporal incidence of prostate cancer. Questionnaire was also administered to 120 prostate cancer patients to establish the risk factor habits associated with cancer in Ibadan metropolis. The study objectives are to examine how some socioeconomic characteristics have predisposed patients to the modifiable risk factors and examine the spatial variation in the incidence rate of prostate cancer among the five local government areas for a period of 20 years (1993–2012). The findings of the study show that income and level of education have a significant influence on predisposing people to the modifiable risk factors of smoking, alcohol consumption, physical inactivity, animal fat intake, red meat consumption, and calcium intake. Time-series analysis presents a strong positive relationship in the incidence of prostate cancer. This shows that the income status and educational status of patients play an integral role as a risk factor for prostate cancer in the Ibadan metropolis. Secondary evidence presented shows that the built environment (industrialization, pollution effect) in the sampled local government areas (LGAs) plays a vital role in the rate of dwellers' exposure to cancer.

Keywords Spatio-temporal Incidence · Prostate Cancer · Risk factor · Socioeconomic characteristics · University College Hospital Ibadan

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1 Introduction

Human mortality across Third World countries is a reflection of disease exposure such as cancer. Cancer of the prostate, malignancy of the prostate gland (a walnut-sized organ located under the bladder in males), is now recognized as one of the most important medical problems facing the male population. Prostate cancer is the fourth most common cancer in the world, the second most common cancer, and the fifth cause of death among men (Parkin et al. 2005; International Agency for Research on Cancer IARC 2012). According to IARC (2012), 15% (1.1 million) of the diagnosed incidences of cancer among men is prostate cancer related to a mortality rate of 19–24 persons per 100,000 in Sub-Saharan Africa.

Despite its prevalence, there are large geographic variations in incidence rates of prostate cancer. For example, in Sweden, where there is a long life expectancy and mortality from smoking-related diseases is relatively modest, prostate cancer is the most common malignancy in males, accounting for 37% of all new cases of cancer in 2004 (Persson et al. 2005). However, African-American men have a 47% higher incidence and a 128% higher mortality than white men in the same geographical location (Baquet et al. 1991). Studies (Baquet et al. 1991; Parkin and Muir 1992; Ogunbiyi and Shittu 1999) stated that the variations in prostate cancer in Africa show that the Eastern, Western, and Southern African countries can be said to be in the top 10 milestones in cancer incidences.

Prostate cancer has become the number 1 cancer in Nigerian men and constitutes 11% of all male cancers (Terwase et al. 2014). Due to the limited screening programs in Nigeria, the number of prostate cancer cases has increased. The known risk factors probably contribute to a varying degree among Nigerians, who are generally of average build or in the low-normal range for body mass index (Ogunbiyi and Shittu 1999). Kamangar et al. (2006) opine that despite the lack of verifiable and definitive etiological evidence, diet remains the main etiology factor of prostate cancer. High intake of animal fat, meat (Kolonel 2001), and calcium (Chan et al. 2001) had been associated with an increased risk of prostate cancer.

In Nigeria, the University College Hospital in Ibadan has been the major center for the management of cancer cases. This is due to her initial acquisition of cesium, radiotherapy suite, and a CAT scanner. With a service range of Nigeria and surrounding West African countries, the hospital has had an official cancer registry since 1960. The register shows increase in death over the years. The death rate of prostate cancer had shown a steady decline all over the world in recent years, but in Nigeria and other African countries, the reverse was the case (AllAfrica, 25 March 2012); out of whom 80% of men with prostate cancer in Nigeria were over 65 years of age (PM News, 26 March 2012).

Recent observations indicate that there has been a changing trend in cancer incidence in Nigeria. Therefore, this study is concerned with an examination of the socioeconomic factors that predispose sufferers within the metropolis of Ibadan to the disease. We based this study on the concept of human ecology of disease, which focused on human behavior, in its cultural and socioeconomic contexts, and interacts

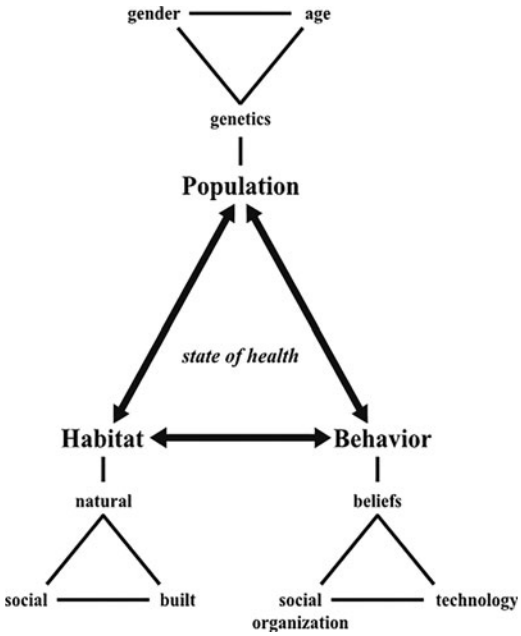

Fig. 1 The triangle of human ecology of disease. (Source: Meade and Earickson 2000)

with environmental conditions to produce or prevent disease among susceptible people. The three dimensions of habitat, population, and behavior form a triangular model of human ecology and underlie disease etiology, consequences, and prevention (Fig. 1).

2 Research Methodology

Based on cross-sectional epidemiological study, a mixed approach that focused on both primary and secondary data was used in this study. The primary data on the socioeconomic variables of prostate cancer patients and the risk factors of the disease among patients were obtained using a questionnaire. Questionnaire administration exercise was carried out, targeted at the prostate cancer patients at the treatment facility (which is also a referral facility), University College Hospital, Ibadan. The secondary data on prostate cancer cases within Ibadan metropolis from 1993 to 2012 and male population were sourced from the medical records for prostate cancer cases at the Cancer Registry, Pathology Department, situated in the University College Hospital (UCH), Ibadan, and National Population Commission, Ibadan, respectively. As obtained from the cancer registry, the figure stood at about 370 patients as of May 2013. Given an estimated population of about 370, a sample size of 120 respondents was purposively selected to represent the total population.

The sampling technique was selected based on the people considered appropriate for the study and because there is a limited number of people who serve as the target of the study. Copies of this questionnaire were administered to the patients at the hospital premises on Monday and Thursday of every week, the days for clinical and procedural appointments, based on the number of patients available on the appointment days with ethical considerations well managed.

Descriptive statistics, and frequency distribution, was used to present and explain the socioeconomic characteristics of the respondents. Also, the socioeconomic variables of income and level of education were cross-tabulated against the modifiable risk factors to have an understanding of how they influence on the predisposition of patients to the modifiable risk factors. The significance of the relationships was examined using chi-square analysis option with the strength of the association tested using Cramer's V.

The incidence rate for the metropolis was calculated using the formula (Number of new cancer cases/population) $\times$ K; where K $=$ 100,000, and the rate expressed per 100,000 male population. Analysis of variance (ANOVA) was used to analyze the variation because the independent variable (Location) has five categorical levels, and the dependent variable (Incidence rate) is continuous. Necessary statistical tests such as Levene's test of homogeneity, appropriate post hoc test (Games–Howell to be precise), and measure of association were carried out to ascertain if equal variance was assumed or not, ascertain where the observed differences in the means actually lie, and to ascertain the strength of the relationship between the independent and the dependent variables. As regards the trend analysis, the absolute figures for observed new cases of prostate cancer were used to run a time-series analysis for the metropolis as a unit and each of the local government as separate entities. From the trend analysis, a trend line of best fit and its associated regression model was derived. From this model, the annual rates of change (increase or decrease, but increase in the case of this study) were derived for each spatial unit.

3 Findings and Discussions

3.1 Socioeconomic Characteristics of Respondents with Prostate Cancer

The data captured shows that majority (85%) of the sampled respondents whom are prostate cancer patient are men aged between 50 and 69 years. The proportion (7.5%) observed among men between 40 and 49 years may be due to limited screening, sensitization, and testing, which may help in early detection and treatment of the ailment. Supporting the findings, studies (Ishola and Omole 2016; Farazi et al. 2018; Bello et al. 2019) iterated that limited and weak screening exercises, lack of screening equipment, understaffing of experts, and poor sensitization are factors that limit the awareness and early detection of cancer (prostate inclusive). Also, the low proportion observed among 70–79 and above may be due to a relatively small proportion of the population living up to that age and beyond. As the World Health Organization (2018) reported, the life expectancy age in Nigeria is 54.7 years. This explains why the majority of the patients are between 50 and 59 years of age. This aligns with the views of Platz and Giovannussi (2006) that the only well- established risk factors for prostate cancer are older age, black race/ethnicity, and a family history of the disease. Although a majority of the sampled patients are married (62.5%), engaged in the agricultural sector (25%), and have the highest educational certification of 75%. The sector of occupation was also reflected in the 40% majority earning below ₦18,000. This brings to the fore the place of efficient health service financing due to the poor state of the patients as the case may be in the study.

3.2 Spatial Variation of Incidence Rates of Prostate Cancer Among the LGA

Incidence, which refers to the number of cases of a disease diagnosed or reported for a population during a defined period of time (most commonly a year), is presented in Table 1 for the Ibadan metropolis and the local government areas that make it up. The data patient captured as extracted from the raw data obtained from the Ibadan cancer registry, University College Hospital, Ibadan per LGA, is presented in Fig. 1.

Figure 2 conveys information about the risk of contracting prostate cancer within the metropolis. In 1993, Ibadan north local government area showed the highest risk of contracting prostate cancer, followed by Ibadan northwest, then Ibadan southeast; to Ibadan southwest and with Ibadan northeast having the lowest risk of contracting the disease. In Ibadan north local government area, the figure increased but later declined only to jump to a value higher than the year proceeding the year of decline (1995).

Table 1 Correlation analysis of the increase of prostate cancer over time in Ibadan metropolis

		Ibadan metropolis	Time (in years)
Ibadan metropolis	Pearson's correlation	1	0.897**
	Sig. (2-tailed)		0.000
	N	20	20
Time (in years)	Pearson's correlation	0.897**	
	Sig. (2-tailed)	0.000	
	N	20	20

Source: Authors' analysis
[a]Correlation is significant at the 0.01 level (2-tailed)

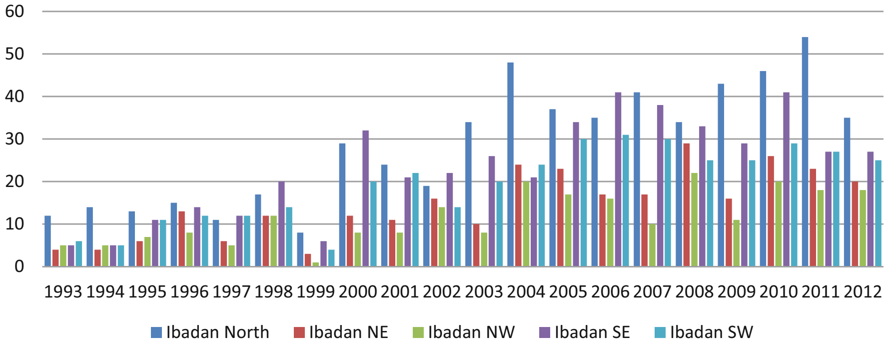

Fig. 2 Reported cases of cancer in each LGA. (Source: Authors' extraction from prostate cancer registers (UCH))

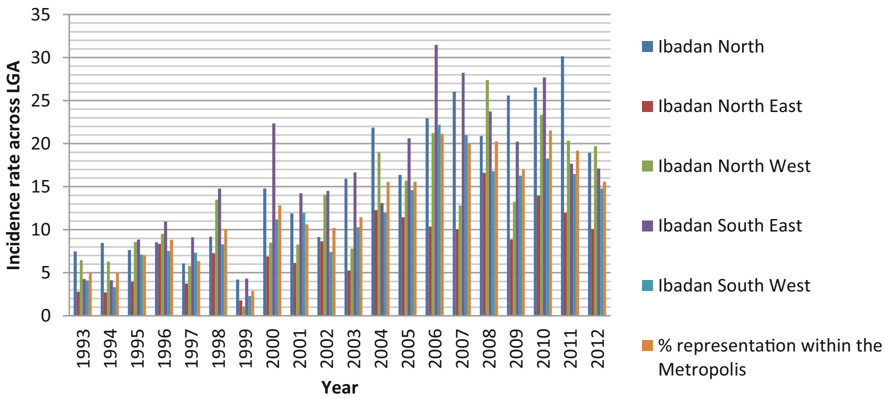

Fig. 3 Incidence rate per 100,000 male population by LGA in Ibadan metropolis 1993–2012. (Source: Authors' computation)

From Figs. 2 and 3, the general trend has shown that the risk of having prostate cancer is on the increase as the value has moved from single-digit values to values in tens. In Ibadan northeast, the value has also been on the increase. Similarly, in Ibadan northwest, Ibadan southeast, and Ibadan southwest, the incidence rate has also been on the increase. A closer look at the table reveals that the rate of increase of the risk of contracting the disease in Ibadan northeast is not as high as the risk in other local government areas until in the 2000s, however, with a slight rise and fall. Urbanization remains an underlying contributory factor for the reported increase in incidence rate.

To further query the incidence rate of prostate cancer in Ibadan metropolis over time, see Fig. 3.

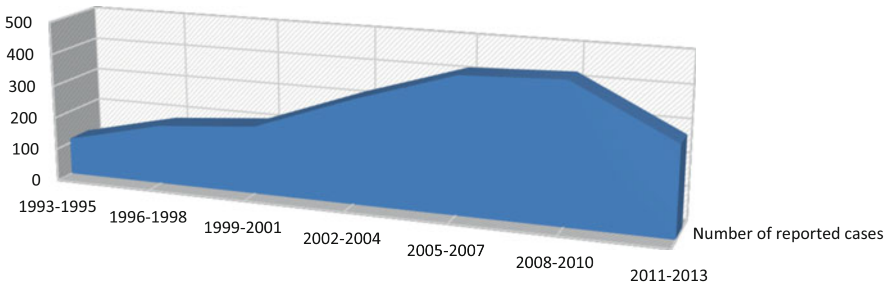

Fig. 4 A 3-year average analysis of reported prostate cancer cases in UCH Ibadan. (Source: Authors' analysis)

From the analysis, the year 1999 from the hospital register had the history of the lowest reported 22 prostate cancer cases, and the year 2010 with the highest sitting at 162 reported cases. Considering a 3-year interval timeline analysis, that analysis shows that years 2008–2010 had the highest reported cases. It was revealed from the study, as presented in Fig. 4, that the post-millennium era accounted for 74.1% (1440 reported cases) out of 1945 total registered prostate cancer cases. Evidence from the post-millennial events shows that there was a sudden spike in reported cases in the year 2000, which subsequently declined in the years 2001–2003. The pre-millennium era accounted for only 545 reported cases. The lower reported cases can be attributed to the functioning of the medical delivery machine and possible declining cases of health reporting in Ibadan.

Unbundling the urban population across the sampled LGAs over time shows that Ibadan north with 569 reported cases had the highest cases recorded in the register followed by Ibadan southeast (465 cases), Ibadan southwest (386 cases), Ibadan northeast (292 cases), and Ibadan northwest with 233 cases, respectively. In the time-series analysis of prostate cancer incidence (1993–2012), the data on the observed new cases, absolute incidence, in the study area was used for the trend and pattern of movement analysis of the observed new cases of prostate cancer to be on the increase. This is to say that the incidence of prostate cancer within the study area is on the increase, although some years tend to witness a decline (Fig. 5). A 3-year average analysis shows a steady increase from 1993 to 2007 and a steady rate of reported incidence between 2007 and 2010. Thereafter, a decline in reported cases continues to dive down to the year 2013.

The regression equation derived from the trend line, as shown in Fig. 5, shows an increase in the rate of the incidence. The regression model from this relationship is $y = 25.7 + 6.8143x$. The average annual rate of increase for the metropolis is 6.47%. The study hypothesizes that there is no significant increase in the incidence of prostate cancer cases in Ibadan metropolis over time. The significance test in Table 1 shows a 0.897 correlation coefficient between incidence and time. Also, in the time-series analysis are the regression model, coefficient of determination, and

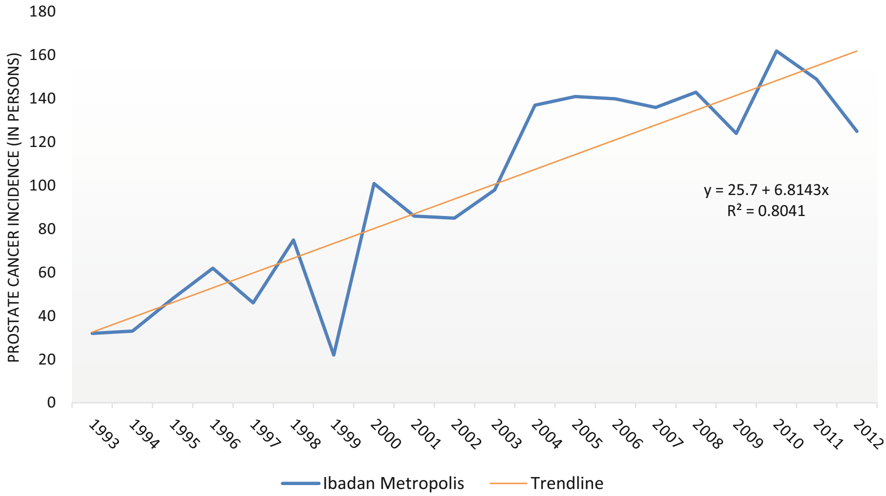

Fig. 5 Trend analysis of the incidence of prostate cancer in Ibadan metropolis. (Source: Authors' analysis)

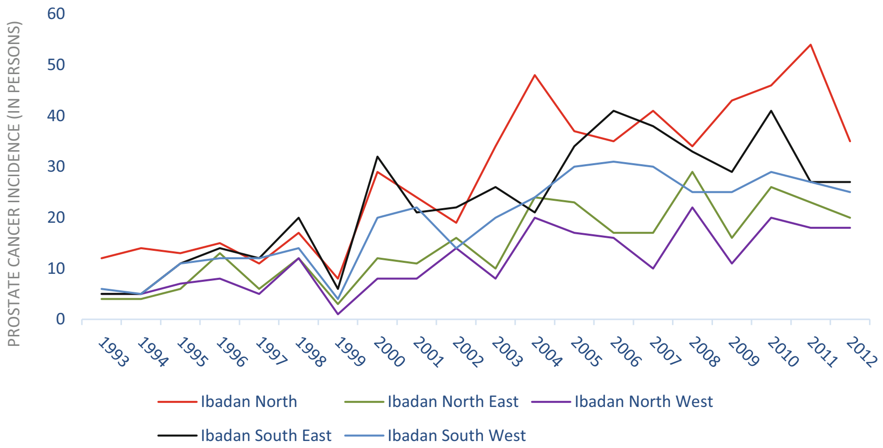

Fig. 6 Trend of prostate cancer for local government areas in Ibadan metropolis. (Source: Authors' analysis)

rates of change for the five local governments. This is to say that there is a strong positive relationship. In a nutshell, this connotes that the increase in the incidence of prostate cancer over time is a strong relationship that tends to increase with time.

The pictorial time analysis of the combined pattern of movement of prostate cancer for all the local government areas within the metropolis is also shown in Fig. 6.

This trend shows an upward movement for all the local government areas over time. Ibadan north ranks highest in magnitude, followed by Ibadan southeast, Ibadan southwest, Ibadan northeast, and lowest in Ibadan northwest. From the analysis according to LGA, the trend and regression line of best fit of prostate cancer were in the Ibadan north local government. This trend shows a fluctuating but upward movement of prostate cancer in the administrative unit. This movement has a strong positive relationship of 0.8690 (square root of the coefficient of determination, R^2) with time. Besides, the rate of increase of the incidence stands at 1.97% over time. In Ibadan northeast, the trend and regression line of best fit show a fluctuating but upward movement of prostate cancer in the administrative unit. This movement has a strong positive relationship of 0.8223 with time and a 1.04% increase in the rate of incidence.

As for Ibadan northwest local government area (Fig. 6), the trend shows a fluctuating but upward movement of prostate cancer in the administrative unit. This movement has a strong positive relationship of 0.7677 with time and a 0.7507% incidence increase. The analysis from the data revealed that in Ibadan southeast and Ibadan southwest local government area, the trend shows a fluctuating but upward movement of prostate cancer in the administrative unit. This movement has a strong positive relationship of 0.8018 and 0.8587 with time with an incidence increase rate of 1.4921% and 1.228% over time, respectively.

From the findings as presented in Table 2, Ibadan north LGA (1.97) recorded the highest rate of increase, followed by Ibadan southeast (1.49), Ibadan southwest (1.22), Ibadan northeast (1.03), and Ibadan northwest (0.75) LGA in this order. Within the metropolitan Ibadan, the rate of increase in the incidence of prostate cancer stands at 6.4736%. The study set out to test the hypothesis that there is a significant difference in the means of incidence rates among the local governments. The hypothesis of the significance in the spatial variation observed in the incidence rate was tested using two-way ANOVA. The analysis, as presented in Table 2, shows F ratio and Levene's test of homogeneity as significant at $p < 0.05$. A Games–Howell's post hoc examination was further carried out, and the analysis shows that differences in the means occurred between Ibadan north and Ibadan northeast and between Ibadan southeast and Ibadan northeast. The measure of association, Eta, shows a typical relationship between locations and incidence rate of prostate cancer. The spatial variation among the local governments has an F ratio that is significant at $p^{< 0.05,\ F}0.05^{(4,\ 95)} = 4.691$. The observed difference in the means occurred between Ibadan north and Ibadan northeast ($\pm$ 7.47250) and between Ibadan southeast and Ibadan northeast ($\pm$ 8.04400). The strength of association between locations and incidence rate showed a moderate association.

Table 2 Descriptive of ANOVA of spatial variation in disease incidence in LGA

					95% confidence interval for mean				
Location in LGA	N	Mean	Std. deviation	Std. Error	Lower bound	Upper bound	Minimum	Maximum	
Ibadan N	20	15.6295	8.01344	1.79186	11.8791	19.3799	4.20	30.15	
Ibadan NE	20	8.1570	4.04816	0.90520	6.2624	10.0516	1.77	16.60	
Ibadan NW	20	13.1315	6.90730	1.54452	9.8988	16.3642	1.09	27.37	
Ibadan SE	20	16.2010	8.02148	1.79366	12.4468	19.9552	4.14	31.46	
Ibadan SW	20	11.6620	5.77611	1.29158	8.9587	14.3653	2.30	22.20	
Total	100	12.9562	7.20737	0.72074	11.5261	14.3863	1.09	31.46	
Levene's test of homogeneity of variances				**Summary of ANOVA**					
Levene's statistic	df 1	df 2	Sig.		Sum of squares	df	Mean square	F	Sig.
3.113	4	95	0.019	Between groups	848.265	4	212.066	4.691	0.002
				Within groups	4294.403	95	45.204		
				Total	5142.668	99			
Measures of association: Effect size measure of incidence rate and location									
		Eta	Eta squared						
Incidence locations		0.406	0.165						

Source: Authors' analysis

3.3 Socioeconomic Characteristics and Risk Factors of Prostate Cancer

Studies (Boyle and Levin 2008; Mahmood et al. 2012) identified the effect of urbanization as a modifiable risk factor to prostate cancer. It was argued that the socioeconomic status and lifestyle of individuals are factors that contribute to the prevalence of prostate cancer. Education and improved income remain a distinct factor that defines urban areas. This study attempts to explain the relationship between the respondent's risk factors of prostate cancer and socioeconomic variables.

3.4 Education and Prostate Cancer Relationship

There have been arguments that there exists a relationship between education and human health (Link and Phelan 1995; WHO 2008; Zimmerman et al. 2015). Farazi et al. (2018) opine that men of lower education were less likely to be aware of prostate cancer. Following this assertion, this study tests the relationship between income, level of education, and modifiable risk factors of animal fat intake, red meat intake, calcium intake, physical activity, alcohol consumption, and smoking habit (Appendices 1 and 2). To establish this using inferential statistics, the study hypothesizes that there is no significant relationship between the level of education and the modifiable risk factors of prostate cancer.

These study findings iterate the relevance of education in human behaviors. A p-value <0.05 ($\chi 2 = 8.026$) shows that there is a significant relationship between the level of education and smoking habit as modifiable risk factors of prostate cancer. This study argues that there is a high possibility of less sensitization on the place of smoking toward prostate cancer. The effect size measure, Cramer's V, shows a minimal statistically significant association between the two variables of 0.45. The place of smoking as probabilistic risk factors toward an individual development of prostate cancer is also identified (Meister 2002). Gilman et al. (2008) sermonized that there exists an undeniable relationship between a person's educational status and the risk of smoking.

Further established is the association between alcohol consumption and cancer-related issues (Turati et al. 2013; Nelson et al. 2013). Reavley et al. (2011) mentioned that education indirectly reduces alcohol consumption. The analysis aligns with this study evidence of a low probability level ($p < 0.05$) and Pearson's $\chi 2$ (9.888) value, indicating that it is unlikely that the two variables are independent. The analysis also shows that there is a relationship between the level of education, physical activities, animal fat intake, and calcium intake as modifiable risk factors of prostate cancer.

3.5 Average Monthly Income and Prostate Cancer Relationship

The relevance of patient income to life expectancy, type of disease exposure, and health status relationship cannot be underplayed (Ettner 1996; Benzeval et al. 2000). To explain if income explains prostate cancer risk incidence, we carried out a chi-square analysis between patients' income, smoking habit, physical exercise, alcohol consumption, calcium, and red meat intake (see Appendix 2). The study shows a relationship between income, physical activity, calcium intake, red meat intake, and animal fat intake. The strength of the relationships is 0.453, 0.455, 0.550, and 0.432, respectively. The relevance of income to the exposure to prostate cancer was identified by Bello et al. (2019). In their study, they argued that the high- income earners (above poverty level) are more likely to be more sensitized as to the relevance of early screening and more likely to go for testing. This argument speaks of health service and infrastructure access and affordability. Connecting the dot of the income effect, Osayomi and Orhiere (2017) in urban Ibadan opined that obesity could be traced to increase dependence on fast food. While the study did not investigate the level of patronization of fast foods by patients, the authors argue that the income composition of the respondents, the majority (60%) of who earn beyond the ₦18,000 minimum wage, gives an edge to patronize such eateries.

Further argued in this study is the ethnic characterization and alignment with red meat intake. Okunlola (2012), in the study of meat consumption within the south-western region of Nigeria, reported that the price and palatability define the choice of meat to patronize. To be noted is the increased preference for processing, frying, and smoking in the form of *suya* (an assorted form of smoked spiced red meat). The effect of this is the increased exposure to fats and smoke, which further poses a threat to prostate cancer incidence. Ogunwole and Adedeji (2014) argued that there exists a high dependence on red meat consumption in Ibadan as many (71.3% of the sample) cannot eat without meat. Even among households, it was revealed that the demand for meat is generally high in this region (Adetunji and Rauf 2012).

3.6 Ibadan Built Environment and Prostrate Cancer Incidence

The built environment of the sampled area of the study is the five metropolitan LGAs. Ibadan metropolis comprises diverse built environments that are the public/ institutional or occupational and the residential built environments. The built space activities pose various risk exposure among residents.

3.7 Occupational Risk Environments and Prostate Cancer

The work environment in the metropolis of Ibadan varies based on availability and accessibility. These environments are peculiar to certain carcinogenic substances based on the activities carried out, which can contribute to the incident rate of prostate cancer. Pollutants from industries and diverse chemicals emitted from activities and practices tend to pollute the environment, which in turn has side effects in the long run on the people within the industries and sectors. This is in accordance with studies carried out by Enander et al. 2004 and Mark and James 2010, who reported that the global health problems in most developing countries could be linked to the continuous exposure of workers to these toxic metals.

3.8 Industrial Occupation Contribution to Prostate Cancer Exposure

We argue that people working within industrial zones are vulnerable to pollutants that can increase the risk of prostate cancer and other associated diseases. Omotesho (2019) was of the view that technicians in the automobile industry are among the set of people most exposed to occupational and environmental pollution risk that can cause prostate cancer due to high exposure to lead and cadmium, among others. Such pollutants, in turn, are among the risky contributors to the pollution of the environment, most importantly in developing countries including Nigeria.

3.9 Agricultural Occupation Contribution to Prostate Cancer Exposure

Farming, as one of the occupations of participants in the studied area Ibadan metropolis, has a gliding effect as well as poses risk and exposes the farmer to prostate cancer. Based on existing studies that have been carried out, farming remains classified as a contributor to occupation risk for prostate cancer (Blair et al. 1992; Parent and Siemiatycki 2001). Farm owner and employee are exposed to toxic substances like herbicides, insecticides, fertilizers, and others used on the farm to boost the productivity of crop and tend to be at high risk as these are the contributing factors (Alavanja et al. 2003). It was examined that pesticides, planting of crops and raising of livestock, equipment used for personal protective methods of pesticide application used, other agricultural activities, and exposures at a high rate can contribute to the incident rate of prostate cancer. All these remain peculiar farm input activities among urban farmers in Ibadan (Wahab and Popoola 2018).

3.10 Residential Environments and Prostate Cancer Exposure

The residential built environment of Ibadan metropolis located in the industrial zone, characterized by poor ventilation, and use of extensive use of fuelwood all contribute to prostate cancer exposure in Ibadan metropolis. Adelekan and Jerome (2006) earlier reported an increase in household use of fuelwood in Ibadan. This, according to Olugbire et al. (2016), is common among low-income households of the state. The increasing fuelwood demand coupled with poor ventilation (Fakunle et al. 2016, 2018) increases residents' exposure to prostate cancer.

3.11 Conclusion and Recommendation

Degenerative diseases continue to threaten the livelihood of urban dwellers. Prostate cancer as a degenerative disease contributes to the increasing global mortality. Some of the causal factors are geographical, some are socioeconomical, and some are often a relationship between the socioeconomic– geographical–locational factors. Findings based on captured socioeconomic variable of prostate cancer in Ibadan metropolis show that socioeconomic variables of income and level of education have a significant influence on predisposing people to the modifiable risk factors of smoking, alcohol consumption, physical inactivity, animal fat intake, and calcium intake; except for smoking, which shows no statistical significance with income. This shows that the income status and educational status of patients play an integral role as a risk factor to prostate cancer in Ibadan metropolis.

Sequel to this, it is imperative to understand that sensitization programs should be carried out by the government at all tiers to make people aware of the risk factors of this degenerative disease and how the modifiable risk factors could be avoided or reduced to the barest minimum. Also, people should be sensitized on early PSA testing. It is believed that early detection through the test will reduce morbidity and improve life expectancy and better health-care management. Although this may increase the incidence figure, since the PSA test is capable of detecting growth in the gland when it is asymptomatic, it will forestall an increase in mortality cases. A better method of disease case recording should be adopted in order to make available data that will assist researchers in delivering more detailed findings. Moreover, a proper system of data collection from health facilities in and around the tertiary health facility should be put in place.

The relevance of improved exercise and controlled fat consumption as a means of reducing the possibility of prostate cancer needs to be well explored among the patients and residents of Ibadan. As the unspoken culture of Nigerian men, definition of wealth as how much of meat a man consumes should be checked and well sensitization offered toward controlling red meat intake.

Appendices

Appendix 1 Relationship Between Education and Modifiable Risk Factors

Smoking by level of education							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	8.026[a]	3	0.045	Nominal by nominal	Phi	0.259	0.045
Likelihood ratio	8.157	3	0.043		Cramer's V	0.259	0.045
Linear-by-linear association	6.760	1	0.009	N of valid cases		120	
N of valid cases	120						
Alcohol consumption by level of education							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	9.888[a]	3	0.020	Nominal by nominal	Phi	0.287	0.020
Likelihood ratio	15.194	3	0.002		Cramer's V	0.287	0.020
Linear-by-linear association	7.621	1	0.006	N of valid cases		120	
N of valid cases	120						
Physical activity by level of education							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson chi-square	83.601[a]	12	0.000	Nominal by nominal	Phi	0.835	0.000
Likelihood ratio	91.508	12	0.000		Cramer's V	0.482	0.000
Linear-by-linear association	2.897	1	0.089	N of valid cases		120	
N of valid cases	120						
Animal fat intake by level of education							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	88.664[a]	9	0.000	Nominal by nominal	Phi	0.860	0.000
Likelihood ratio	96.041	9	0.000		Cramer's V	0.496	0.000

(continued)

Linear-by-linear association	3.819	1	0.051	N of valid cases		120	
N of valid cases	120						
Red meat intake by level of education							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	43.321[a]	6	0.000	Nominal by nominal	Phi	0.601	0.000
Likelihood ratio	41.543	6	0.000		Cramer' s V	0.425	0.000
Linear-by-linear association	3.085	1	0.079	N of valid cases		120	
N of valid cases	120						

Appendix 2 Relationship Between Monthly Income and Selected Modifiable Risk Factors

Alcohol consumption by income							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	9.019[a]	3	0.029	Nominal by nominal	Phi	0.274	0.029
Likelihood ratio	11.847	3	0.008		Cramer's V	0.274	0.029
Linear-by-linear association	4.658	1	0.031	N of valid cases		120	
N of valid cases	120						
Physical activity by income							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	73.939[a]	12	0.000	Nominal by nominal	Phi	0.785	0.000
Likelihood ratio	80.876	12	0.000		Cramer's V	0.453	0.000
Linear-by-linear association	2.055	1	0.152	N of valid cases		120	
N of valid cases	120						

(continued)

Calcium intake by income							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	74.375[a]	9	0.000	Nominal by nominal	Phi	0.787	0.000
Likelihood ratio	84.587	9	0.000		Cramer's V	0.416	0.455
Linear-by-linear association	0.189	1	0.663	N of valid cases		120	
N of valid cases	120						
Red meat intake by income							
Chi-square tests				**Symmetric measures**			
	Value	df	Asymp. sig. (2-sided)			Value	Approx. sig.
Pearson's chi-square	72.553[a]	6	0.000	Nominal by nominal	Phi	0.778	0.000
Likelihood ratio	55.200	6	0.000		Cramer's V	0.550	0.000
Linear-by-linear association	0.019	1	0.890	N of valid cases		120	
N of valid cases	120						

Source: Authors' analysis

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Emerging Nonthermal Techniques for Food Processing

Hassan Nabeel Ashraf, Muhammad Atif Randhawa, Hafiz Ahmad Toor, and Noman Walayat

Abstract In food processing industries, thermal processing is a traditional method to kill the microorganisms and provision of safe food for human consumption. This develops some desirable characteristics in a final product, like caramelization and browning. On the other hand, it also develops some undesirable changes in color, flavor, natural freshness, and losses of micronutrients such as vitamins and phenolic contents. These days consumers are aware and conscious about their health, hence and demand safe and nutrients rich food products is increasing day by day. Minimum or mild heat treatment is the best solution for meeting consumer expectations because it minimizes the losses of beneficial properties of the final product and retains maximum natural color, flavor, texture, and freshness attributes of the final products. No significant effect was reported in phenolic contents, ascorbic acid, and other heat-sensitive nutrients during non-thermal processing. This chapter discussed the nonthermal processing techniques in detail and its effects on micronutrients, texture, and microbial load of processed foods.

Keywords High-pressure · Phenolic contents · Irradiation · Natural freshness · Pathogenic bacteria · Electromagnetic spectrum · UV light

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1 Introduction

It is estimated that the nearly one-fourth part (25%) of all food is lost after harvesting due to spoilage, damage, vermin, insects, improper handling, lack of proper storage infrastructure, and transportation (Mostafavi et al. 2012). Traditionally, thermal processing is used for microbial elimination, textural softening, aroma-component formation, protein coagulation, and starch swelling. During processing, some undesirable changes occur, for example, loss of bioactive compounds, vitamins, natural flavor, coloring pigment, and freshness (Fellow 2009). The losses of bioactive compounds depend on unsaturated structure and chemical composition of the respective food. Dissolved oxygen is another important factor that increases the degradation of food bioactive compounds during heating (Rawson et al. 2011).

During pasteurization of degassed tamarillo nectar at 80, 90, and 95 °C for 10 min, the vitamin C is stable but the hydroascorbic acid rapidly decreases. Whereas the ascorbic acid decreases and hydroascorbic acid is completely destroyed in nondegassed samples. Thermal processing does not much affect the total carotenoid, but some degradation was observed in 5, 8-epoxidation and *cis*-isomerization of carotenoids. The losses in ascorbic acid contents due to the oxidation and prolonged exposure time that generate free radicals may speed up degradation (Rawson et al. 2011).

In the last few years, consumers have become interested in high nutritional food that has natural sensational properties such as taste, flavors, freshness, and color. Mild heat or minimum processing techniques are ideal techniques that meet consumers' needs. It retains maximum heat-sensitive micronutrients and natural attributes such as color and flavor as compared to thermal processing methods (Shankar et al. 2014). This chapter reviews the nonthermal processing technique (high hydrostatic pressure, ultrasound, pulse electric field, and irradiation) and its effect on food matrix, texture, microbial load, and shelf life.

2 High Hydrostatic Processing (HHP)

Mainly, high hydrostatic pressure processing (HHP) is suitable for solid and liquid food in packaging or without packaging. The normal pressure applied ranges between 100 and 800 MPa (Jan et al. 2017) along with temperature ranges below 0 °C to above 100 °C for few a seconds to 20 min. HHP is an emerging method against microbial elimination, enzyme activation or inactivation, gel formation, and protein denaturation or modification. pH and water activity are critical parameters for microbial inactivation. The inactivation of food spoilage microbes and pathogens are rapidly increasing at temperature range between 45–50 °C. Generally, temperature range (90–110 °C) along with 100–900 MPa pressure are used for inactivation of spore-forming bacteria, for example, *Clostridium botulinum* (Jan et al. 2017; Yikmis 2016).

Generally, it eliminates the microbial growth in vegetable products, meat products, crustaceans, fruit juices, and beverage industries are achieved at the range of 100–900 MPa. At the same conditions are used to it achieves other valuable objectives like vitamin stability (in vegetables, beverages, and fruit juices), frozen meat thawing, bitterness in grapefruit juice, chocolate hardening, and starch and protein gelatinization (Yikmis 2016).

2.1 Principle

High-pressure technique depends on two major principles. First is the Le Chatelier's principle, addresses the equilibrium stages, its behavior while applying pressure during treatment, changes in molecular configuration and phase transition. Second is Isostatic Principle, addresses the uniform distribution of pressure in all directions. The ideal hydrostatic conditions are directly depends on time and space. It can be developed when a fluid is used to transmit the pressure throughout the food. In HHP application, the pressure and its effects are homogenously distribute within food products, even any size and geometry of the food products (Abera 2019).

During HHP, the final texture of the food cannot change because it applies equal pressure in all directions of the food product. For example, if we press grapes with hand, it becomes a juice because of applied uneven pressure. In first stage, take grapes in a bottle and fill with water, put a lid on it, and then apply pressure with the hand as much as we can, no change is observed in shape because the pressure around the grapes is homogeneous. So, different pressure ranges affect the cell structure, which is a major reason for the destruction of microorganisms in high-pressure processing. In next step, drains the water from the container, moves the food for drying, and then gets packed (Howson 2019; Ramaswamy et al. 2008; Yaldagard et al. 2008).

2.2 HHP Effects on Foods

Protein denaturation play an important role in the inactivation of microbial activity due to the agglomeration of cellular protein and enzymes inactivation. The cell membranes are destabilized at high pressure due to phase transition and no effect on permeability. The denaturation of protein depends on these factors like salt and sugar concentration, water activity, pH (Boja et al. 2012), processing temperature, pressure, and time. Processing at high temperatures and pressure has a significant effect on vegetative bacteria (Heinz and Buckow 2010).

Chiao et al. (2014) reported the effect of HHP on off-flavor compound and microbial growth during 16 days refrigeration storage of raw octopus. The chopped octopus was treated in lab-scale high-pressure equipment at 150, 200, 450, and 600 MPa for 6 min at refrigerated temperature. During 16 days storage study, psychotropic bacteria were reduced by 0.1 CFU/g at 150 MPa, 0.5 CFU/g at 300 MPa, 1.3 CFU/g at 450 MPa, and 2.8 CFU/g at 600 MPa as compared with control sample. The production of dimethylamine (DMA) and trimethylamine (TMA) was significantly reduced at 600 MPa as compared with reference sample. After 12 days, the biogenic amines (BAs) arise up 1.82 mg/g in control, 1.40 mg/g in 450 MPa treated sample, and 1.35 mg/g in 600 MPa treated sample were reported. The growth rate and reproduction are decreased at 10-50 MPa, whereas inactivation done at higher temperature (Radnemacher 2006).

Kyung et al. (2014) worked on flavor compounds, biochemical activity, and physicochemical properties of garlic extract by controlling pH and time. HHP-treated garlic extract at 1.8–3 pH significantly reduced pungent smell as compared to other treatments. The antimicrobial, antitumor, and antioxidant activities decreased as compared to control. This rapidly reduced antioxidant and microbial activity investigated after 3 min, and no antitumor activity was shown at this stage.

Kadar (2008) evaluated the effect of storage stability and sensory properties of mango cubes at 300 and 600 MPa for 1 min to increased shelf life up to 9 weeks at 3 °C. During storage, the fresh flavor properties was decrease but overall no significant changing was observed in sensory and color attributes, and increased the prevention of microbial growth as compared to control.

During 9 days of storage, the total soluble solid decreased from 16.4% to 14.8% and 15.8% to 13.2% at the 200-MPa in treated and untreated samples, respectively. However, no noticeable changing was observe in the 400 MPa and 600 MPa treated samples. The 200 MPa treated sample significantly decreased ascorbic acid contents and increasing the titratable acidity as compared to control, and no significant change was observed in the 400 Mpa and 600-MPa-treated samples. The reduction of ascorbic acid mainly due to the oxidation and prolonged sterilization affects of ultra-high pressure (UHP). Previous research showed that the food products are more microbiologically stable if treated more than 400 MPa. Scientists suggested that if food treated at 600 MPa is more effective in increasing shelf life and retains the fresh-cut Chinese yum slice quality during storage (Guangjie and Bo 2000).

Patras et al. (2009) were assessed the HHP effect on phenolic contents in blackberry and strawberry puree. Phenolic contents (939 mg/100 g DW) were observed 9.8% increase in strawberry puree at 600 MPa, no noticeably increase was observed in untreated puree (855 mg/100 g DW). The same trend was seen in the blackberry puree. The total phenolic contents may be increased due to extractability of some antioxidant components at high-pressure processing.

3 Pulses UV Light Technology

Pulses UV light is used to inactivate the microbial load by using a short intensive spectrum of white light 200–280 nm (Gomer-Lopez et al. 2007), visible light 400–700 nm, and near-infrared light 700–1100 nm (Palgan et al. 2011). UV light generator (including power unit, a chamber transfer light source to high power intensity pulse, timer control, and trigger generator) are produces high intensity electric pulses to minimize the microbial growth (Heinrich et al. 2016; Ozer and Demirci 2006).

3.1 Mechanisms and Its Effect on Microorganisms

The main target of pulsed light in photochemical mechanism is nucleic acid (deoxyribonucleic acid). UV light is absorb by C-C double bonds in protein and nucleic acid that induces the antimicrobial effect as resultant it changes the DNA and RNA structure, which interrupt the transcription and translation in DNA and causes cell death (Gayan et al. 2014; Cheigh et al. 2012).

Can et al. (2014) investigated the UV effect on microbial growth in cheese sample. The packed and unpacked cheese were treated with UV (200–600 nm for 40 s at 5 cm), after the analysis results showed that the UV treatment effectively inhibited the growth of *Listeria monocytogenes* (*L. monocytogenes*) and *Penicillium roqueforti* (*P. roqueforti*). The maximum inactivation of *P. roqueforti* and *L. monocytogenes* was reported 1.32 and 1.24 log CFU/cm and 2.9 and 2.8 log CFU/cm, respectively. No significant effect was observed on lipid oxidation and color degradation when cheese was treated for 5 s at 13 cm as compared to untreated cheese.

Keklik et al. (2010) illustrated that the effectiveness of UV pulse on *Salmonella* in vacuum packed and unpacked chicken breast. The chicken breast was treated for 60 s at 5 cm. The elimination of *salmonella* was (2.4 and 2.4 log CFU/cm^2) reported in unpacked and vacuumed packed, respectively, and no significant changing was observe in color and chemical composition when chicken was treated with UV light for at 5–60 s for 5–13 cm ($P < 0.05$).

However, some studies reported that the effect of UV light pulse on texture and color are depend on the distance between sample surface, lamp, and energy dose (Orlowska et al. 2013). Rough or uneven surface and pores in foodstuff (like grain, cereals, and spices) effectively reduce the efficiency of UV light on microorganisms. Some studies on pulses UV light treatments and their effect on microbes are discussed in Table 1.

4 Pulsed Electric Field

Pulsed electric field (PEF) is another minimum food processing technique, in which suitable concentrations of electric pulses are used to eliminate the microbial load with minimum effects on food. PEF is retain maximum physical and sensorial attributes of the final product and reduces undesirable changes like browning and color degradation (Syed et al. 2017).

Table 1 Microbial load eliminated by using pulses UV light in some food products

Food product	Microorganisms	Treatment	Log reduction CUF/ml	References
Milk	*S. aureus*	3 pulses/s and 1.27 J/cm^2/pulses, 20–40 m/min flow rate, 5–11 cm distance	0.55–7.23	Krishnamurthy et al. (2007)
	E. coli	7–20 J/cm^2/pulses, 3 Hz and 360 μs, 1.17 J/cm^2/pulses, 200–300 nm, a at distance of 2.5 cm	0.61–1.06	Palgan et al. (2011)
	L. innocua		0.51–0.84	
	S. Typhimurium		0.51–1.73	
Apple juice	*E. coli*	1.21 J/cm^2/pulses, 3 pulses/s (pulses width 360 μs) of 100–1100 nm width	4	Pataro et al. (2011)
	L innocua		2.98	
Sugar syrup	*B. subtilis spores*	Pulses width 250 μs: Fluence 1.5 J/cm^2	4.2	Chaine et al. (2012)
	S. cerevisiae	Fluence Pulses 1.23 J/cm^2	5.4	
	A. niger	Fluence Pulses 1.86 J/cm^2	1.3	
Fresh cut melon	*Enterobacteriaceae*	UV-C 20 W/m^2, 10 min: Fluence Pulses 1200 J/cm^2 Fluence Pulses 6000 J/cm^2 Fluence Pulses 12,000 J/cm^2	2.61 2.32 2.14	Manzocco et al. (2011)
Spinach	*L. innocua*	180–1100 nm with 17% of UV light, time 0.3 μs, and fluence pulses 8 J/cm^2	1.85	Aguero et al. (2016)
	E. coli		1.72	
Eggshells	*S. Enterica* sub sp.	200–1100 nm with 8, 12 and 20% of UV light fluence pulses 2.1 J/cm^2	5 log CUF/shell egg	Lasagabaster et al. (2011)
	Enterica serova			
	Typhimurium			
Fish products	*P. Phosphoreum*	High-intensity pulses 325 μs, 200–1100 nm with 8, 12, and 20% UV light fluence pulse 0.053 J/cm^2	5	Lasagabaster and De-Maranon (2012)
	S. Liquefacien		3.9	
	S. Putrefaciens		2.1	
	B. Thermosphacta		<1	

PEF has various applied applications in the food industry for liquid, semi-liquid, and solid food products treatment. A high voltage pulse are use to slowdown/completely eliminated the microbial activity in liquid foods like juices, egg, and dairy products (Qin et al. 1995). In the past, the industries just focus on food safety issues of food quality, acceptability, and composition during drying, dehydration, extraction, and processing efficiencies (Vorobiev et al. 2005).

Short-voltage pulses (μs) generate electric fields ranging between 5 and 50 kV/cm and temperature lower than the thermal conventional methods. The microbial inactivation is a result of the depolarization and permeabilization of the microbial membranes (Wouters et al. 2001). Only bacterial spores are resisting during PEF treatment, but vegetative cells of the yeast and bacteria are killed. PEF mainly focuses on the control of spoilage, pathogenic microbes, and extends the shelf life of different foods without the usage of preservatives and heat treatments to make better nutritional, qualitative, and sensorial profiles by utilizing energy in an economical and efficient manner (Hodgins et al. 2002).

4.1 Mechanisms of PEF

The higher concentration of the electric field used from a few microseconds to milliseconds with an intensity range of 10–80 kV/cm. Generally, electric pulses are produced between two electrodes to properly maintain the treatment gap. There are numbers of different forms in which electric field is applied such as bipolar waves, oscillatory pulses, or decaying waves. Temperature is applied in different ranges such as above-ambient, sub-ambient, and ambient temperatures. After treatment with PEF, food is generally packed at refrigeration conditions (Mohamed and Eissa 2012).

PEF works between the set of electrodes that generating high voltage by maintaining the treatment gap as well as the suitability of controlling/monitoring devices (Zimmermann and Benz 1980). Food products are placed in the treatment chambers with non-conductive surroundings, which is why the electric field does not flow from one side to another. In this way, high voltage and concentrated signals have produced a force that demage the cell membrane of the microorganisms (e.g., bacteria) (Reddy and Penchalaraju 2014; Fernandez-Diaz et al. 2000). The cell membrane become depolarized and permeabilized (Wouters et al. 2001). Only bacterial spores are resisting during PEF treatment but bacterial and yeast vegetative cells are killed. The main focus of PEF to control the spoilage, pathogenic microbes and extend the product life without the using of preservative to make better nutritional, qualitative, and sensorial rich product (Hodgins et al. 2002).

4.2 Impact and Applications

Pasteurization of the food products such as dairy, juices, liquid eggs, and soups is extensively treated by PEF. For the treatment purpose, the product should not have air bubbles, contain lower electrical charges, and particle size should be lower than the recommended size and treatment gap between the electrodes. PEF is also used for the extraction of different bioactive and heat-sensitive compounds like antioxidants and phenolic compounds (Siemer et al. 2015).

The viscosity of the product have much importance in pulse electric field treatment. PEF is preferably applied to the less viscous fruit juices that have less electrical conductivity such as cranberry, citrus, and apple juices. Researchers found that less browning ratio was observed in PEF-treated citrus juice (stored at 4 °C for 112 days) as compared to traditional pasteurized juice (browning due to conversion of ascorbic acid to furfural) (Yeom et al. 2000). Furthermore, functional components, texture, flavor, microbial growth rate, and shelf life in PEF-treated juice remained constant as compared to traditional processing. PEF technology is used in various fields, for example, food preservation, modification of enzymatic activity, and increased drying efficiency, extraction, and wastewater treatment (Ade-Omowaye et al. 2001).

This technique was applied to break down biological tissue and increase the extraction from intracellular compounds such as pectin, which is traditionally extracted from fruits by enzymatic reactions. Short pulses are applied to avoid undesirable electrolytic reactions and excessive heat loss that increase the extraction of pectin from the pomace (Min et al. 2007). PEF preferable improves the enzyme releasing and glycolysis that are important factors for proteolysis and meat tenderization (O'Dowd et al. 2013). Another experiment reported in which bacterial load was reduced up to 5–6 log at 22–28 kV/cm with 50 °C for 17–101 μs to inactivate Gram-positive and Gram-negative bacteria in the whole milk (Guerrero-Beltrán et al. 2010).

5 Irradiation

In which, food are treated with ionizing radiation like gamma rays that are emitted from X-rays, radioisotopes ^{137}Cs and ^{60}Co, and high-energy electrons. These rays enhance the shelf life, disinfestations, safety aspects of the food by eliminating insects/foodborne pathogens, and decreasing the microbial load in fruits, nuts, vegetables, animal-based products, and cut flowers (Marcotte 2001).

Likewise, milk pasteurization and canning of vegetables and fruits, irradiation make ensures the safety and quality aspects of the final product. Losses are reduced during storage; as well as, shelf life, parasitological and microbiological safety are improved after irradiation. Nowadays, various nonfood items such as medical products, cosmetics, hospital supplies, packaging material, and wine corks are being irradiated. For measurement, the absorbed gamma rays in the product are calculated in Grays (Gy). Mostly, the order of the treatment levels is 1–10 kGy (1 kGy = 1000 Gy) (Mostafavi et al. 2012):

$$1\ \text{Gy} = \text{absorbed energy}\ (1\ \text{Joule})/\text{kg of product}$$

Food irradiation is considered as a mild treatment of the food in which radiation dose approximately 1 kGy, generally radiation dose increases the product's temperature up to 0.36 °C. In contrast, heating, cooling, and drying cause high nutritional losses and formation of carcinogenic aromatics, and heterocyclic compounds at high-temperature treatment but still not reported in any irradiated foods (Tomlins 2008). International bodies such as the International Atomic Energy Agency (IAEA), Codex Alimentarius Commission (CAC), Food and Agriculture Organization (FAO), and World Health Organization (WHO) have worked on different projects to focus on the quality, shelf life, and safety aspects of the different irradiated food products (Farkas 2006). The sensitivity of the radiation depended on irradiation temperature, moisture content, ability to recover from radiation injury, chemical and physical structures of organisms. Researchers reported after long-term studies on animal feeding that sterilized foods or radiation-pasteurized foods are nutritious and safe for humans (Thayer and Boyd, 1999). On the other hand, some foods are sensitive to irradiation such as grapes, cucumber, and tomatoes. Nowadays, in more than 60 countries food irradiation is applicable to many food products.

5.1 Principle

When food is exposed in an ionizing radiation environment for treatment, at this point chemical bonds absorb some energy. Some chemical bonding are breakdown and produces free radicals, which are highly unstable and reactive. Resultantly, these compounds are react with nearby compounds and produce radiolytic just like. thermolytic compounds that are produce by heating. Generally, 1 kGy ionizing radiation is rupture to one bond per million of the compounds (Jung et al. 2015). The specific character of the ionizing irradiation has an impact on microbial and plant cells due to the exposure of DNAs. This phenomenon leads to breakage of DNA strands, cross-linking, and base damage. Finally, organisms lost the ability to reproduce. There are three main sources of the radiation that are approved for food irradiations.

Gamma Rays These are emitted in radioactive form from the cesium (cesium 137 with the energy of 0.66 MeV) and cobalt (cobalt 60 element with the energy of 1.17 and 1.33 MeV). G-rays have more penetration power than electron beams, so it is easily to treat the bulk food packaging. Routinely, G-rays are used to sterilize households, dental treatment, medical products, and cancer treatment are achieve by these rays (Hvizdzak et al. 2010).

X-Rays These are produced by the reflection of electrons (accelerated machine) that contains high-energy stream off heavy metal. Bremsstrahlung (electromagnetic X-rays) are produced by the high-energy electrons generated from a source, for example, X-ray machines. These rays have ability such as "quantitative availability," which makes them commercially useful, no residue of radioactivity into packaging material, and achieved desired food-preservative effects. X-rays have high penetration power so it is use for pellet size containers. X-rays are generally applied in medicinal and other industries to gain the internal structure of images (Farkas 2006).

E-Beam or Electron Beam These are similar to X-rays containing high-energy electrons sourced from an accelerator. These accelerated electrons have low penetration power (10 MeV) than gamma and X-rays in highly perishable foods. Although, ionizing electromagnetic irradiations and electrons have different penetration power into food furthermore electron have less conversion rate into X-ray (approximately less than 10%) and this has hindered the use of this type of radiation source so far (Mostafavi et al., 2012).

5.2 Effect and Applications in the Food Industry

The main commodities that are irradiated bulb crops, tubers, dried ingredients, poultry, meat, fish, and fruit (Molins 2001). The potential values of food safety and prevention are achieved by controlling food poisoning pathogens. The subjected food is sterilized with irradiation concentration 10 kGy or above. However, the lower concentration (1–10 kGy) are used for food pasteurization (Farkas 2006). These also work as a disinfection source for insects at < 1 kGy, as a sprout inhibitor in onion and potatoes at < 0.5 kGy, as a ripening inhibitor in fruits at < 0.3 kGy, and cause trichinosis elimination in pork at < 1.0 kGy (Table 2) (Li et al. 2017).

Irradiated food has not become popular among the public due to lack of awareness about irradiated food and less availability in the market. However, irradiation can provide safe and free food from any type of health risks. Many studies have been reported that the irradiation process does not produce any radioactive compound in the food matrix nor changes the nutritional and sensory profile of food like taste, appearance, or texture. Actually, the changes that occurred due to irradiation are negotiable and hardly of judgment to predict (Molins 2001).

Table 2 Irradiation application in foods

Advantages	Dosage (kGy)	Irradiated food products
High dosage (10–50 kGy)[a]		
Industrial sterilization and mild heat	30–50	Meat, poultry, seafood, prepared foods, and sterilized hospital diets
Food additives decontamination	10–50	Spices, enzyme preparations, natural gum, and ingredients
Medium dosage (1–10 kGy)		
Shelf-life increasing	1.0–3.0	Fresh fish, strawberries, mushrooms, etc.
Microbial Elimination	1.0–7.0	Fresh and frozen seafood, raw or frozen poultry and meat
Improving quality and safety parameter	2.0–7.0	Grapes (increasing juice yield), dehydrated vegetables (reduced cooking time), etc.
Low dosage (up to 1 kGy)		
Sprouting inhibition	0.05–0.15	Potatoes, onions, garlic, root ginger, yam, etc.
Insect and parasite disinfection	0.15–0.5	Cereals and pulses, fresh and dried fruits, dried fish and meat, fresh pork, etc.
Physiological processes delay	0.25–1.0	Fresh fruits and vegetables.

[a] Only used for the special purpose, the joint FAO/WHO Codex Alimentarius Commission has not endorsed high-dose application (WHO 1988)

6 Conclusion

Generally, nonthermal processing techniques are inactivate the enzyme, eliminate microorganisms, ensure the safety and quality standards, and meet the consumer preferences and needs. It also retains the maximum volatile compounds and natural properties in the final food product as compared to thermal processing. Nonthermal techniques could be used for developing functional or smart food. It is time and energy effective as compared to thermal or other tradiational methods. So, in order to obtain healthier and better qualitative foods, then it will be combined with other techniques. For example, raw materials are treated with pulsed electric field before drying or freezing to become more efficient and also improve the overall quality.

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Food Hazards and Brain Development: The Case of Cadmium

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Abstract Accumulation of environmental contaminants like heavy metals in food is a major source of human exposure. Their adverse effects are well documented, but there is little information about the health problems arising from their exposure during critical periods of life of development. The aim of the chapter was to examine the possible neurotoxic effects after exposure of pregnant females and lactating mothers and their pups to different heavy metals in order to evaluate the possible dysfunctions.

Keywords Neurotoxic effects · Exposure · Food · Heavy metals · Accumulation · Pregnant females · Lactating mothers

1 Introduction

Great evidence shows now the presence of growing negative impact of environmental degradation on contamination of the food chain and consequently led to the development of chronic diseases like cancer, diabetes, reproductive disorders, obesity, and brain development disorders (WHO 2001).

With large-scale utilization, diverse applications and potential environmental release their risk to ecological environment and/or human health.

While the sources of pollution or exposure likely to contribute to the deterioration of health are multiple, the great challenge of toxicology concerns the assessment of chronic exposure to a multitude of chemicals. Indeed, the population is rarely exposed acutely to a single pollutant at a time, and consistent epidemiological research examines environmental pollutants one by one ignoring chronic exposure to multiple environmental pollutants as they constitute an integral part of the food chain. The approach of considering therefore chronic exposure to chemicals ranging from trace metals and pesticides to polychlorinated biphenyls to pharmaceuticals and

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personal care products is fully justified. Recently, a multitude of studies has concerned the effect of a mixture of heavy metals on physiological and biochemical parameters. These exposures of the mixture can sometimes be detrimental to the organism, even at very low concentrations, and with an unobservable toxic effect but whose cocktail effect is rather toxic (Beyer et al. 2014).

The censorship of the accumulation of exposures and their interactions is therefore necessary to better reflect reality, particularly over time, and we then speak of an exposome. This notion requires taking into account the “window of exposure” and the periods of life when the individual is more vulnerable. This is the case with the impact of chemical pollution on health with exposure during the in utero period, which is now widely recognized by the scientific community.

More generally, protecting the periods of pregnancy and infancy in the face of environmental exposure appears to be a priority. Epidemiological studies have reported that more and more children suffer from neurodevelopmental and behavioral alterations linked to environmental exposure.

It should be remembered in this regard that the physiology of the adult central nervous system (CNS) differs from that of the developing CNS. In fact, the neurotransmitters that modulate synaptic transmission in adults during brain development will interact with their receptors to influence the formation of the architecture of different regions and different structures of the brain. This is the case with the environmental substance, which is neurotoxic via an action on neurotransmission systems such as heavy metals, which could therefore impact variously the brain of adults and that of young people. In adults, it is known that neurotoxicity affects the peripheral nervous system more easily because the CNS is protected from a series of chemicals by the blood–brain barrier (Costa et al. 2004). However, some metals appear to be likely to pass through this barrier and reach the CNS (Costa et al. 2008).

An important aspect of the toxicology of heavy metals is to study their effect on the general physiology and that is particularly related to nervous system during development. This aspect of developmental toxicology related in this review will concern both exposures to cadmium in utero and during postnatal period. It will also involve understanding the cellular mechanisms of action of the heavy metal, leading to functional and neurochemical alterations during the development of experimental animal brain and/or human.

2 Cadmium Characteristics and Toxicity

Cadmium is a nonessential heavy metal with the most common oxidation state, Cd^{2+}, as the most common form. In contrast to other heavy metals, it is not a widely distributed metal in the environment but is extensively used in industry and also in daily life (principally by cigarette smoking actively or passively and by food) that provides easy exposure to human beings. Concerning food, it is noteworthy that phosphate fertilizers have been identified as an important source of cadmium in arable land, where it tends to accumulate over time (Mortvedt 1987). Crops tend to take up cadmium from the soil, and the cadmium content of foodstuffs, the main source of cadmium uptake by humans, has become a concern for human health. Furthermore, foods, especially seafood (oysters, crustaceans, and fish), can concentrate cadmium 10,000–100,000 times compared to seawater. Other elements also provide significant amounts of cadmium such as cereals, dairy products, and meats, especially kidneys and liver. Contamination secondary to the preparation and packaging of food cannot be ruled out (González-Weller et al. 2006). Concerning smoking, a cigarette contains 1–2 μg of cadmium, of which about 10% can be absorbed by inhalation. In smokers, the quantity of cadmium entering the body through the lungs varies from 0.7 μg of cadmium, in a user of 10 cigarettes per day, to 4.2 μg of cadmium, in a user of 60 cigarettes per day (Roels and Lauwerys 1983), whose exposure is in the form of fine particles of cadmium oxide, which can be deposited in the pulmonary alveoli. Tobacco is unique in its tendency to concentrate cadmium; its concentration in leaves is significantly higher than that of fruits, earnings, and vegetables (Gairola et al. 1992). Besides, its use in batteries, accumulators, or in alkaline electric cells (80%) and in pigments of paints or plastics (10%) constitutes additional sources of contamination. The toxicity of the metal has been well documented, and its harmful effects arise in the organisms rapidly notably in low concentrations due to its low excretion rate and also to its half-life in the body that is approximately 20–40 years and by consequent is mainly stored in the liver and kidney (Nawrot et al. 2010; Pretto et al. 2014). Interestingly, it has been reported that the worldwide dietary Cd intake ranges from 10 to 40 μg/day to several hundred in Cd-polluted regions (Jomova and Valko 2011).

After its absorption, plasmatic cadmium is bound to high molecular weight proteins, notably albumin (Nordberg and Nordberg 1987). It is then rapidly distributed to the liver where it induces the synthesis of a low molecular weight transport protein rich in sulfhydryl (SH) groups: metallothionein (MT) with which it has a high affinity. The formation of Cd-MT complexes neutralizes the toxic effects of cadmium. The Cd-MT complex is then redistributed in all organs, especially in the kidneys (Nordberg and Nordberg 1987). This Cd-MT complex is finally excreted after glomerular filtration, unlike the Cd-albumin complex, which does not pass the glomerular barrier due to its high molecular weight. In kidney tubular cells, MT is then destroyed by lysosomal enzymes, releasing consequent $Cd^{2\ +}$ ions into the cytoplasm. The cytoplasmic Cd^{2+} is then bound again to a newly synthesized MT in the cytoplasm. When the MT production capacities are exceeded, cadmium exerts renal tubular toxic effects, leading to higher renal cadmium concentration in the renal cortex than in the renal medullary zone.

On the other hand, the nervous system (SN) in general and the central nervous system (CNS) in particular are also sensitive to the effects of Cd, like other nonessential heavy metals (Malqui et al. 2018). The effect is even more pronounced during in utero formation and its various functional maturation stages (pre- and postnatal) as embryotoxic and fetotoxic effects associated with exposure to cadmium (Cd) have also been described (Hazelhoff Roelfzema et al. 1987) as a result of partially efficient placenta barrier (Korpela et al. 1986; Needham et al. 2011) against this meta and the immaturity of the blood–brain barrier (BBB). Indeed, under normal

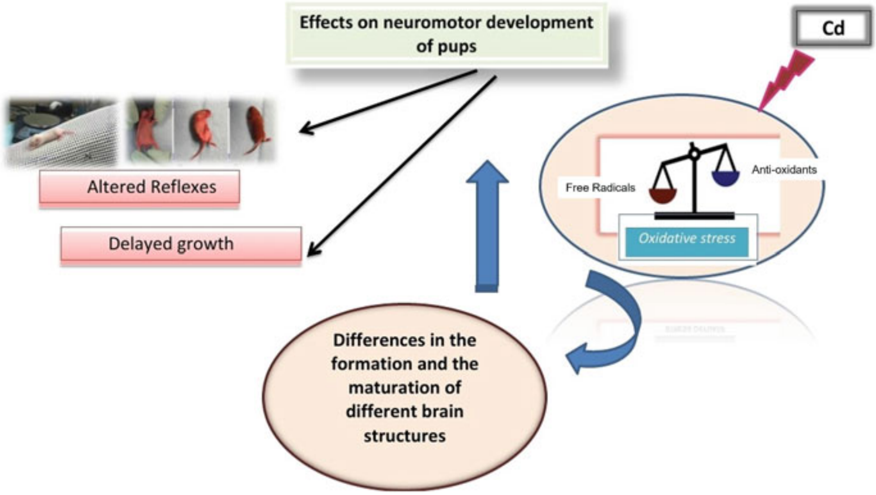

Fig. 1 Proposition of eventual mechanism of cadmium (Cd) on neurodevelopmental dysfunction

conditions, Cd barely reaches the brain in adults due to the presence of BBB; however, this structure is not fully developed in young animals, and studies have shown that Cd can increase the permeability of BBB in rats (Shukla 1987) to enter and accumulate in the brain rats during development and in adult rats as well (Mendez-Armenta 2007). Furthermore, the anatomical and physiological components of the choroid plexuses become the target of xenobiotics; hence, Cd tends to accumulate in the choroid plexus at concentrations much greater than those found in cerebrospinal fluid (CSF) and elsewhere in brain tissue. A study led in humans revealed that the concentration of Cd in the choroid plexuses was about 2–3 times greater than that seen in the cerebral cortex (Manton 1984). As a general choroid plexus toxicant, Cd can directly damage the choroid plexus ultrastructure. Due to the differences in the integrity of the BBB (Antonio 2003), Cd is therefore considered to be more toxic to neonates and young rats than to adult rats (Fig. 1).

3 Developmental Neurotoxicity

There is another form of neurotoxicity that is another way of disrupting the function and integrity of the CNS, called developmental neurotoxicity (Rodier 1995). Indeed, during development, the brain is particularly sensitive to a series of disruptors, which can lead to a whole series of persistent structural and functional alterations.

Brain development can be disturbed by certain antiepileptic drugs, ethanol from alcoholic beverages (Costa et al. 2004), nicotine (Slotkin 2004, 2008), and fluorides (a natural contaminant in water) as well than by a series of industrial substances such as heavy metals, namely, methylmercury, arsenic, cadmium, aluminum, or even lead.

The list of products and substances capable of altering brain development may grow longer with the studies concerning them.

4 Particular Sensitivity of the Developing Brain

One reason the developing CNS is more sensitive to neurotoxic substances than when it reaches maturity is because it is more likely to be exposed to toxicants. In fact, first of all, the blood–meningeal barrier does not complete its formation until late: it does not end in humans until 6 months after birth, leaving the door open to toxins (Adinolfi 1985; Rodier 1995).

Second, the role of the placental barrier is also insufficient to prevent the entry of many chemicals into the body and brain (Andersen et al. 2000).

Third, metabolic capacities and therefore detoxification mechanisms reach maturity only after birth: end of the second to the third week after birth in rats and from the second to the third month after birth in humans (Ginsberg et al. 2004).

Fourth, another phenomenon related to detoxification causes the developing brain to be more susceptible to neurotoxic drugs. In fact, Cd can interact with a series of serum proteins (albumin), which, through this interaction, reduce its ability to reach the brain (Kousba et al. 2004). However, the concentration of these serum proteins is low during development and increases with age to play a more effective role in adults. For example, in rats, their concentration increases from 7% to 12% of postnatal day 4 to 90 postnatal days (Mortensen et al. 1998).

Another reason for the particular sensitivity of the developing brain to toxins is the complexity of development and the very low possible repair capacities of this organ. In fact, during fetal life, a few dorsal embryonic ectodermal cells must quickly form billions of specialized, highly interconnected cells. In addition, to achieve optimal development, neurons must migrate through specific processes, from their point of origin to a specific, assigned location, to establish nerve connections. Each of these brain development processes must take place both at a time and in a specific order (Rodier 1995; Rice and Barone 2000; Bjorling-Poulsen et al. 2008). Any disruption of each of the processes during brain development can lead to disturbances in its functioning in adults, disorders that may prove to be irreversible and therefore persistent because there is little repair capacity in the adult brain (Grandjean and Landrigan 2006).

5 Maternal Behavior

For the recovery test, the females treated with the mixture or with Cd took longer to recover and bring all the pups back to the nest compared to the controls. Pregnant females treated with aluminum chloride were significantly lower in weight compared to controls (Ghorbel et al. 2016).

Likewise, water consumption was significantly affected by exposure to lead during the gestational stage (Bunn et al. 2001) and to aluminum (Ghorbel et al. 2016), which may therefore point to the role of these elements in this decrease. All the results clearly demonstrate that maternal behavior remains highly sensitive to the effect of trace heavy metals, which strongly argue for the sensitivity of the gestation period and to a second degree of lactational period.

6 Effect of Cadmium on Morphological Parameters After Delivery

Studies in rodents have shown that during pregnancy, maternal stress due to restraint, noise, light, and heat may be associated with adverse effects in the mother and be detrimental to embryonic/fetal development and postnatal (Golub and Domingo 1996; Miller et al. 2002; Nishio et al. 2001). In addition, it is also well known that exposure to certain metals during pregnancy can also cause developmental toxicities (Domingo 2001) and adverse birth outcomes in human, such as preterm birth, low birth weight, and small gestational age (Zhang et al. 2020). Furthermore, it has been reported that prenatal exposure to 100 mg/kg/day Al, alone or associated with a restraint stress, induces a reduction in body weight from the 12th postnatal day and delays in eruptions of the incisors and sexual maturation (testicular descent). In recent decades, several studies concerning metals have confirmed that the mixture of different metals induces a decrease in body weight in rats (Su et al. 2017; Colomina et al. 2005).

Concerning the body weight during the postnatal period, it has been reported that the group of treated pups exposed to cadmium chloride during gestation and lactation, measured during this postnatal phase, was significantly lower than that of the control group. This difference in weight may be correlated with the high cadmium concentration in the placenta and the fact that pregnant rats giving birth to low birth weight babies have high cadmium levels in the placenta (Llanos and Ronco 2009). Prenatal exposure to 50 ppm cadmium induces a significant decrease in body weight of pups compared to unexposed rats (Ronco et al. 2009), but not a decrease in rats exposed to 30 ppm (Ronco et al. 2009), indicating that the relationship between Cd exposure and birth weight depends directly on the exposure dose as well as the route of administration. Interestingly, the World Health Organization (WHO) (2001) confirmed that the birth weight of newborns was significantly lower after maternal exposure to cadmium.

Concerning physical parameters, Kamel et al. (2011) observed that there was no significant difference concerning the appearance of hair, the detachment of the ears, and the opening of the eyes in the pups treated compared to the controls, against which there were significant differences between groups regarding incisor eruption.

When body length is considered, results are contradictory. Thus, the decrease in body length of offspring exposed to Cd during gestation and lactation, including males and females, was significantly lesser than that observed in controls (Xue et al. 2015), who report that Cd may be related to fetal development or postnatal growth. On the other hand, conflicting data have been reported when pregnant mice received cadmium chloride in drinking water during lactation, from PN1 to PN17. These studies indicate that there are no significant differences between the control group and the Cd-exposed group for body weight during the postnatal period in males (Petersson Grawe et al. 2004); these differences may be related to periods of exposure.

It has been shown that prenatal exposure to 100 mg/kg/day of Al, alone or associated with restraining stress, induces a decrease in body weight from PN12, a delay in incisor eruptions and sexual maturation (testicular descent). In recent decades, several studies done on metals have confirmed that mixing several metals induces a decrease in body weight in rats (Hong et al. 2017).

A delay in the neuromotor and behavioral development of the newborn (neonatal reflexes) in terms of righting reflex (surface righting reflex) and negative geotaxis has been reported in offspring of female rats exposed to 0.02–0.04 mg kg^{-1} during gestation (Environment Agency, EA) (2009).

Several studies have linked increased locomotor activity to hyperactivity in pups exposed to Cd from birth to 30 days after birth and that a low dose of Cd exposure in rats resulted in significant hyperactivity after 30 days of postnatal life, followed by coma in adult rats (Rastogi et al. 1971). This effect of Cd, this window time, would be due to bioaccumulation of the metal.

Kamel et al. (2011) had already shown, in some experiments with the same exposure dose, that cadmium chloride caused a significant increase in the level of anxiety in offspring exposed to gestation and lactation. Several studies indicate that anxiety is regulated by the gabaergic (GABA) and serotonergic (5-HT) systems. In this regard, an increase in GABA activity decreases anxiety, and a decrease in 5-HT neurotransmission leads to anxiolytic effects (Chopin and Briley 1987). It has been reported that chronic exposure to Cd in humans causes headaches, sleep disturbances, changes in eating behavior, and memory deficits; evidence indicates that GABA and 5-HT are involved, most in addition to the regulation of these CNS functions (Minetti and Reale 2006). It therefore seems likely that exposure to Cd leads to changes in the GABA and 5-HT systems that may be responsible for these effects.

On the other hand, dysfunction of antioxidant system could also occur for the harmful effects of cadmium during this sensitive period as has been reported for other environmental contaminants (Ouardi et al. 2019). The majority of previous studies of these enzymes (CAT, GPX, GST, SOD) in the whole brain of newborn or adult rats exposed to cadmium in vivo, or in vitro, have revealed a decrease in their activity (Ahammadsahib et al. 1987; Antonio et al. 2003; Zhang et al. 2009), although there are conflicting data (increased activity) in vivo and in vitro (Carageorgiou et al. 2004–2005; Liapi et al. 2013) (depending on the doses administered or the routes of administration). The developmental profile of GSH and GPx levels in the brains of newborns showed considerable fluctuations, which may reflect their needs at different stages of development (Shivakumar 1991). Similarly, in the liver and kidney of growing rats, Cd induces an increase in the endogenous levels of lipid peroxides and lipid peroxidation and inhibition of SOD in both the tissues (Hussain et al. 1987).

7 Conclusion

In conclusion, taken altogether, the data given by the previous studies point to the deleterious effects of prenatal and postnatal exposure to cadmium during the gestation phase and during the lactation period on physical and functional developmental aspects of newborns as well as their behavior and their oxidative status. These findings strongly suggest that these abnormalities could be explained by the delayed maturation of the brain due to this contamination occurring early during sensitive periods of formation.

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Obesity in School-Going Adolescents

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Abstract Background and Objectives Overweight and obesity are currently considered a serious public health problem around the world due to their potential health implications and increasing frequency. This chapter aims to conduct a review of the literature on obesity in school-going adolescents.

Conclusion Overweight and obesity are a major public health problem. Preventing obesity requires nutritional education to pay more attention to the quality of your daily food.

Keywords Obesity · Schoolchildren · Overweight

1 Introduction

The prevalence of overweight and obesity has risen at an alarming rate in recent decades, especially among children and adolescents, becoming one of the greatest challenges for public health in the twenty-first century (Reilly 2006a, b; World

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Health Organization 2015). Overweight and obese adolescents are at risk of remaining obese into adulthood. They are also at risk of developing metabolic (diabetes) and cardiovascular diseases at an earlier age (Reilly 2006a, b; Kelishadi 2007). Childhood and adolescent obesity is a global problem that affects developed countries as well as low- and middle-income countries, especially in urban areas (Kelishadi 2007; World Health Organization 2015). This chapter aims to conduct a review of the literature on obesity in school-going adolescents.

2 Definition of Obesity

Obesity is defined as an excess of fat mass; today it is recognized as a public health problem of the twenty-first century because of its prevalence and its rapid evolution in many countries, in adults and children, and the resulting overall cost to society (Kechid et al. 2010).

3 Prevalence of Childhood Obesity

3.1 Prevalence of Childhood Obesity in North Africa

In Morocco, according to the World Health Organization, a cross-sectional study of 1418 schoolchildren aged 8–15 in the public sector of the city of Marrakech shows that the prevalence of overweight and obesity was 8% and 3%, respectively (Sebbani et al. 2013).

In Algeria, as in many developing countries, the prevalence of overweight and obesity tends to increase. Indeed, the survey of children and adolescents aged between 6 and 16 years in the commune of Khroub reports a frequency of 10.2% of overweight including obesity according to the Centers for Disease Control and Prevention (CDC) and 21.6% according to French references (Mekhancha et al. 2005). On the other hand, in children aged between 3 and 13 years, living in the commune of Constantine and Jijel, the prevalence of overweight and obesity is 21.9% (Oulamara 2006). A survey in eastern Algeria reveals that 23.10% of children aged 4–13 are overweight (Taleb et al. 2011).

3.2 Prevalence of Childhood Obesity in Europe and America

In France, childhood obesity alerts health and medical authorities. A study carried out in Lorraine in 1980 shows that 2.5% are obese. This percentage rose to 3.2% 10 years later. In Central West France, the prevalence of obesity in children aged 10 more than doubled in 16 years, from 5.1% to 12.5% (Kechid et al. 2010).

In Stockholm, the prevalence of overweight was 21.6% in 1999 and 20.5% in 2003 with a frequency of 3.2% and 3.8%, respectively, of obese boys. In girls, overweight decreased from 22.1% to 19.2% and obesity from 4.4% to 2.8% (Sundblom et al. 2008). Stamatakis et al. reported in 2010 that the prevalence of obesity and overweight among school-aged children in England has stabilized in recent years.

In the United States, the collective INSERM 2000 Expertise (National Institute for Health and Medical Research) indicates that 22% of children aged 11 are obese and 16.9% of children aged 2–19 are obese, that is, 12.5 million children. The prevalence of obesity in American children differs based on ethnicity. In fact, according to data reported by several studies the prevalence of childhood obesity in the Afro-American population is 21.5%; it is 21.8% in the Hispanic population and 12.3% in non-Hispanic whites.

In 1981, in Canada, the prevalence of overweight and obesity for children aged 15–19 was 14% boys and girls combined; between 2007 and 2009, the latter reached 31% for boys and 25% for girls (Tremblay et al. 2010).

3.3 Prevalence of Childhood Obesity in the Rest of the World

According to the World Health Organization, in 2010, the global prevalence of overweight (obesity included) in children was estimated from an analysis of 450 national cross-sectional surveys in 144 countries, at 43 million children, including 35 million in countries developing, who were considered overweight or obese, 92 million being at risk of overweight. The prevalence of overweight (obesity included) in children increased from 4.2% in 1990 to 6.7% in 2010. This trend is expected to reach 9.1% in 2020, representing approximately 60 million children (De Onis et al. 2010).

A review of secular trends in overweight/obesity in 2006 concluded that the prevalence has increased over the past 2–3 decades in most industrialized countries except Russia, Poland, and low-income countries, especially in urban areas.

The prevalence of overweight and obesity doubled or even tripled between the early 1970s and the late 1990s in Australia, Brazil, Canada, Chile, Finland, France, Germany, Greece, Japan, the United Kingdom, and the United States (Wang and Lobstein 2006).

4 Childhood Overweight and Obesity Measurement and Screening

4.1 The Body Mass Index

The Quételet index is a corpulence index also called the body mass index (BMI). It is calculated according to the formula:

$$\text{BMI}\left(\text{kg/m}^2\right) = \text{weight (kg)/height}\left(\text{m}^2\right)$$

BMI is relatively well correlated with body fat in adults, with coefficients of determination between 0.60 and 0.80 depending on sex, age, and ethnicity (Gallagher et al. 1996; Deurenberg et al. 2001). Other clinical parameters are at least as effective markers of fat mass in adults. Thus, a study in more than 1000 subjects, including those obese, showed that body fat was optimally predicted by the weight/height ratio, while the percentage of body fat was optimally predicted by the weight/height ratio^2 (BMI) (Larsson et al. 2006). In children, the correlations observed between BMI and fat mass depend on age, sex, and puberty stage (Eisenmann et al. 2004; Eto et al. 2004). Studies have shown that the sensitivity of the BMI is in some cases insufficient to accurately diagnose overweight (Mast et al. 2002) or obesity in prepubescent children (Mast et al. 2002; Zimmermann et al. 2004). Despite these reservations, BMI is currently widely used in children, with studies showing a sufficient correlation with body fat (Rolland-Cachera et al. 1984; Zimmermann et al. 2004; Reilly 2006a, b).

4.2 Assessment of Body Fat by Anthropometric Criteria

In different forms of obesity, android, at increased cardiovascular risk, and gynoid, measurements of waist and hip circumference are among the parameters used in adults. In children, the relationship between total and intra-abdominal fat accumulation remains poorly understood. Abdominal perimeters such as the measurement of skin folds are therefore of interest for the interpretation of energy expenditure data (Frelut and Peres 2007).

5 Factors Playing a Role in the Development of Obesity

5.1 Eating Behavior

Rapid changes in behavior and food consumption are currently considered to be major determinants of overweight and obesity. The destructuring of eating patterns can contribute to energy imbalance (Paineau 2009). An increasing number of children and adolescents do not eat breakfast, which has been positively associated with increased BMI (Siega-Riz et al. 1998; Berkey et al. 2003). In addition, increasing snacking would be another element in the breakdown of eating rhythms that can increase the risk of overweight by promoting the consumption of energy-dense foods (Savige et al. 2007). The environment of food intake, in particular the increase in meals taken alone, could also encourage overconsumption of energy (Paineau 2009). A longitudinal study involving a cohort of approximately 8000 children showed that the risk of overweight was inversely correlated with the number of meals eaten as a family (Gable et al. 2007). Recent trends in food consumption show that increasing portion sizes also appear to contribute to increased energy consumption by individuals (Fisher and Kral 2008).

On the other hand, a study carried out in 2003 on 4966 children shows their preference for portions of French fries, meats, and chips higher than the recommendations, leading to a risk of overconsumption, especially in disadvantaged populations or in families who eat in front of the television or in fast-food restaurants (Colapinto et al. 2007). Portion sizes have increased markedly over the past 20 years, especially in the United States (Young and Nestle 2002). The overconsumption of energy-dense foods, linked to the high availability of these foods and their high palatability, can also lead to a positive energy imbalance, especially in children at risk of overweight (Kral et al. 2007).

5.2 Mechanisms Determining Food Intake

5.2.1 Hunger, Satiety, and Fullness

Food intake is a complex, periodic behavior through which an organism derives the nutritional resources necessary for survival from its environment. Hunger and satiety are psychophysiological states that, respectively, trigger or inhibit food consumption. Homeostatic (regulation of blood sugar or body fat reserves) or non-homeostatic (conditions of availability of food in the environment) mechanisms help determine the periodic triggering of food intake. Once a meal is started, the stimulation to eat is gradually reduced by the ingestion of food. This satiation process results in stopping consumption even before the nutrients ingested have been absorbed. The size of meals is determined by an interaction of sensory factors (quality and variety of food stimulation), gastrointestinal signals, and neuroendocrine responses to the arrival of nutrients in the digestive tract. A Pavlovian-type learning mechanism, by which the sensory qualities of the food are associated with the metabolic consequences of ingestion, sets up, for each eater, the repertoire of food tastes and rejections. Satiety, the period of absence of hunger that follows the meal, depends on the nutritional composition of the meal and especially on its energy density. The choice of foods very dense in energy induces low satiety and promotes "passive overconsumption." The mechanisms selected by natural evolution to ensure survival in an environment with limited food resources favor the compensation of energy shortages much better than that of excess. In the context of the current food plethora, the obesity epidemic reflects both a biological disposition and a powerful stimulus to eat induced by the environment (Bellisle 2005).

5.2.2 Adaptation of Food Intake

A child is able to regulate the amount of food he consumes according to their energy density and needs (Birch and Fisher 1998). In a study in infants 6 weeks old, milk consumption increases when it is diluted. They have shown themselves capable of maintaining a constant energy supply during the same meal, the modalities of which were varied. Likewise, when the meal is preceded by a high energy preload, the child eats less (Birch et al. 1993). He learns to associate the flavor of the food with a given energy intake (Birch and Deysher 1986). Children aged 2–5 can also adapt their food intake to balance their energy balance over a period of a few days (Birch et al. 1991). Studies show that there are children who are good regulators, able to quickly modify their food choices to adjust them to their needs, and children who are poor regulators whose adaptation is incomplete (Bellisle 1999; Michaelsen and Jørgensen 1995). Children who are overweight, in particular, are often classified as poor regulators and boys are generally better than girls at this (Johnson and Birch 1994).

5.2.3 Nibbling

Snacking is defined as the consumption of food and drink between meals, including milk drinks, regular soft drinks, as well as food and energy drinks (Savige et al. 2007). The increasing prevalence of snacking has recently been suggested as a potentially important influence on energy regulation in adolescents and adults (Kubik et al. 2005; Bertéus Forslund et al. 2005; Howarth et al. 2007). The prevalence of snacking among adolescents and children varies widely across the world. Also, 87–88% of American teens (ages 12–18) snack at least once a day with drinks contributing about 25% of their daily energy intake (Cross et al. 1994; Dwyer et al. 2001).

Snacking is also commonly associated with adverse health and eating habits (Savige et al. 2007). Children more often choose salty, crunchy foods over healthier foods (Cross et al. 1994). Therefore, snacking is commonly considered to be a contributing factor in the development of overweight and obesity, although studies that have examined the association between snacking and body mass index have shown mixed results (Nicklas et al. 2003; Hampl et al. 2003; Kubik et al. 2005; Howarth et al. 2007).

Snacking may also be associated with less frequent meal consumption, which can be detrimental to health as regular meal patterns are associated with greater dietary diversity, healthy food choices, and better nutrient intakes (Cusatis and Shannon 1996; Haapalahti et al. 2003; Neumark-Sztainer et al. 2003; Sjöberg et al. 2003).

5.3 Socioeconomic, Educational, and Cultural Status

In most Western countries, the frequency of overweight and obesity in children differs significantly depending on the socioeconomic level of parents, probably due to lower physical activity, more sedentary lifestyle, a greater dietary imbalance, and less favorable socio-educational and cultural characteristics in the less favored populations (Vieweg et al. 2007; Richard 2008). In some studies, the educational level of parents is the socioeducational factor most associated with childhood obesity (Klein-Platat et al. 2003; Lamerz et al. 2005). A survey in Ile-de-France showed that the prevalence of excess weight varies from 10% to 25% depending on the level of education of the parents, with the most educated parents being the least affected (Vincelet et al. 2006). The type of habitat also seems to play a role, with collective housing increasing the risk of overweight (Feur et al. 2007). In adults, being in contact with obese people greatly increases the risk of obesity; the chances of becoming obese are increased by 57% if the subject has an obese friend and by 37% if his/her partner is obese (Christakis and Fowler 2007). These social phenomena therefore seem to contribute to the progression of the obesity epidemic, at least in adults (Paineau 2009).

"Obesity is developing in a period of economic and social change, it is part of a process of modernization, acculturation, indeed, the evolution of food accompanies the transformations of our society, it can only be understood in the light of technological, sociological, economic, cultural and even political factors" (Weitz et al. 2012).

5.4 Physiological Variations in Body Size and Adiposity Rebound

During growth, body size varies physiologically. On average, the body builds up in the first year of life, then decreases up to 6 years, and grows again until the end of growth. The decrease in BMI values between 1 and 6 years reflects the physiological decrease in adiposity and body size occurring at this period of life when the clinical impression can sometimes be misleading. Indeed, between 5- and 8-year-old children with a normal build appear rather thin (Thibault and Rolland-Cachera 2003). Note also that at the time of peak corpulence around 1 year the visual appearance of the child may be misinterpreted. The child may appear too fat, although he is of normal build for this age. The rise in the curve that occurs on average from the age of 6 is called the adiposity rebound. The age of adiposity rebound correlates with adiposity in adulthood; the earlier it is, the greater the risk of becoming obese (Rolland-Cachera et al. 1984). The interest in rebound adiposity as a predictive marker of the risk of obesity has been confirmed by various studies carried out in Europe, Australia, and the United States (Whitaker et al. 1998; Dorosty et al. 2000).

5.4.1 Fetal Life

According to the hypothesis of Barker (1995), who proposed the concept of the fetal origin of adult diseases, an unfavorable nutritional environment in utero is able to influence the development, structure, and functions of the viscera. It can be the cause of disease several decades later. It is a kind of programmed susceptibility that makes the individual more sensitive to the effects of the environment. Two critical periods have been described in intrauterine life. In early gestation, exposure of hypothalamic centers to a state of over- or undernourishment may influence the regulation of food intake and growth (Jackson et al. 1996; Flynn et al. 1999; Ravelli et al. 1999). The second period concerns the last months of gestation, during which the differentiation and proliferation of preadipocytes occur. The physiological increase in fat mass represents 30% of the weight gain from the 38th week. Overeating during this period can cause fatty tissue hyperplasia and the subsequent development of obesity. Maternal glucose and amino acids, which can cross the placental barrier, stimulate the secretion of insulin by the fetal pancreas, which increases especially from the 20th week. Fetal hyperinsulinism causes an increase in anabolism and stimulates the growth of fat mass, which seems to be more sensitive to these factors than lean mass. Maternal free fatty acids are the main source of lipids for the development of fetal adipose tissue (Flynn et al. 1999).

5.4.2 Birth Weight

Several studies have shown a linear and positive association between birth weight and later life. It may also be due to correlations with adiposity and lean mass (Rogers et al. 2006).

Additionally, maternal obesity, pregnancy weight gain, and blood sugar levels during pregnancy are positively associated with offspring obesity and metabolic disorders (Catalano and Ehrenberg 2006; Hillier et al. 2007). Unlike positive associations of birth weight with obesity, studies of the major comorbidities of obesity generally report inverse associations of birth weight. For example, 1 kg in excess of birth weight has been associated with a 10–20% lower risk of ischemic heart disease (Huxley et al. 2007) and with 1.5 mmHg lower systolic blood pressure in men and 2.8 mmHg lower in women (Gamborg et al. 2007). The contrasting associations with both low and high birth weight could be explained by the co-existence of two separate life pathways in early obesity and later metabolic disease (Lakshman et al. 2012).

5.4.3 Breastfeeding

Work has reported a significant protective effect of breastfeeding against childhood obesity (Kramer 1981), as well as the risk of type 2 diabetes in childhood and adolescence in high-risk groups (Young et al. 2002).

A study of 32,000 children aged around 3.5 years shows that obesity is lower in breastfed children after adjusting for socioeconomic status, birth weight, and sex (Armstrong et al. 2002). While the longitudinal study by Bergmann et al. (2003) of a cohort of nearly 1000 infants showed no difference in BMI at birth, a high BMI in breastfed babies at 1 month, but after 2 months an increase in BMI and skinfold thickness in babies who were artificial breastfeeding, compared to those who had been breastfed for 2 months or more. After a year, bottle-fed babies had a higher risk of being consistently overweight or obese. At 18 months, the two groups showed little difference in the thickness of the skinfold, but the discrepancies appeared again, with babies who were bottle-fed having a significantly elevated risk of developing excess weight at the age of two up to 6 years (Lobstein et al. 2004).

6 Consequences of Obesity

Obese children are at increased risk for hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, type 2 diabetes, hypertension, respiratory problems, and psychological disturbances during adolescence. Since childhood obesity often continues into adulthood, it can lead to a higher rate of morbidity and mortality from cardiovascular disease, diabetes, disability secondary to arthritis, and certain cancers. Thus, the prevention and treatment of obesity in childhood and adolescence are essential public health issues and an important determinant of health (Claire Leblanc 2002).

6.1 Cardiovascular Risk

Nearly three million young Americans have high blood pressure. Obese children are particularly prone to high blood pressure. Those aged 6–11 with triceps skinfold thickness equal to or greater than the 85th percentile were 2.6 and 1.6 times more likely than their thinner peers to have high systolic and diastolic pressure, respectively (Gortmaker et al. 1987). Hypertension that starts in adolescence continues into adulthood, making it a major public health concern (Andersen and Haraldsdóttir 1993).

Genuine arterial hypertension is rare in obese children and deserves investigation. The diagnosis of obesity must involve an investigation of family cardiovascular risk factors and at least once a lipid assessment to screen for associated dyslipidemia.

Fasting cholesterol and triglyceride levels in obese children and adolescents are generally within normal limits, but decrease with weight loss (Frelut 2009).

6.2 Type 2 Diabetes

Diabetes mellitus (types 1 and 2) currently affects 200 million people around the world, including 48 million Europeans, or 5.1% of the adult population (Gidding 1999). Type 2 diabetes accounts for 85–95% of all diabetes in industrialized countries.

Regarding children and adolescents under the age of 15, 430,000 have type 1 diabetes. Prevalence of type 2 diabetes is increasing among young people. Almost 45% of children with de novo diabetes have a nonimmunological disease (Mouraux and Dorchy 2005).

A family history of type 2 diabetes is characteristic, and obesity is a hallmark, as 85% of affected children are obese at diagnosis. A greater proportion of Indigenous Canadians, African-Americans, Indigenous Americans, and Asians have type 2 diabetes (Young et al. 2000). The usual age of onset is 12–14 years, which corresponds to the relative insulin resistance known to occur during puberty. Rising obesity rates and reduced physical activity rates in this age group also contribute to insulin resistance and may be important risk factors for developing diabetes (Callahan and Mansfield 2000).

6.3 Respiratory Complications and Sleep Disorders

Obesity in children and adolescents is associated with a restrictive respiratory syndrome increased in supine position, especially as the degree of overweight is high. If in doubt, functional respiratory tests should help to sort things out with associated asthma, a frequent occurrence (Frelut 2009). There is evidence to show that obstructive sleep apnea (OSA) is associated with obesity and is very common in children and adolescents. It is well established that obesity can cause or worsen OSA through several potential mechanisms (Ranjani et al. 2014). Sleep apnea should be detected in obese children, even very young. Restless sleep, snoring, pauses in breathing, heavy night sweats, and daytime asthenia are all signs (Frelut 2009).

6.4 Psychosocial Complications

Many psychosocial problems have been shown to be strongly associated with obesity in children and adolescents. These include depression, poor self-image, and difficulty adjusting both in the home and in the social environment. Psychosocial factors act against the child with a weight problem and therefore hamper his growth and development. Overweight and obese teens tend to have poor body image and low self-esteem. Among obese children, appearance is more common and is associated with higher weight concerns, more loneliness, poor self- perception of physical appearance, greater preference for sedentary or isolated activities, and lower preference for social activities (Hayden-Wade et al. 2005). Social isolation and stress could interfere with their learning and lead to depression, anxiety, and/or emotional instability (Ranjani et al. 2014).

6.5 Cancer and Obesity

In a prospective study, Calle et al. (2003) showed that there is a positive association between morbid obesity, that is to say, a BMI $\geq$ 40, and a high rate of death from cancer greater than 52% in men and 62% in women compared to subjects with normal BMI. In both sexes, BMI was positively correlated with death rates from cancer of the esophagus, colon rectum, liver, bladder, pancreas, and kidney. BMI was also correlated with death rate from non-Hodgkin lymphoma and multiple myeloma. According to the authors, being overweight or obese could be responsible for 14% of cancer deaths in men and 20% in women (Paineau 2009). The increase in BMI is associated with a sharp increase in the incidence of endometrial and esophageal cancers, a smaller but significant increase in cancers of the kidney, pancreas, ovary, breast, colon rectum, and an increased incidence of leukemia, multiple myeloma, and non-Hodgkin lymphoma. Overall, a high BMI is associated with an increased incidence of cancer (Reeves et al. 2007).

7 Conclusion

Overweight and obesity are a major public health problem. The prevention of obesity requires nutritional education to pay more attention to the quality of your daily food.

Due to the multiplicity of explanatory factors for this overweight, any prevention policy must be defined on the basis of several levels of intervention and therefore be broken down into prevention targeted at all children and in particular obese.

The actions carried out must be aimed in particular at improving the food supply at school, deepening nutritional information, promoting an active lifestyle, developing the place of physical activity in school and after school, creation and improvement of accessibility to sports equipment, and creation of cycle paths at city level.

In view of the multiplicity and complexity of the factors identified in the current progression of obesity, the actions carried out must be based on a multidisciplinary approach. Thus, the child cannot be guided without taking into account his environment. It therefore seems necessary to promote and multiply partnerships between the various stakeholders concerned at the prevention stage. The fight against obesity mobilizes the institutional sector in the fields of health, national education, associative actors, the economic world, and research. Therefore, the convergence of actions and the complementarity of interventions are essential. In any case, the fight against this scourge must be part of a comprehensive approach to prevention and education. Better coordination must now be sought between school, school medicine, and parents.

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Nutritional Aspects and Neurodegenerative Disorders

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Abstract During the last century, a considerable change in the way we eat has taken place in connection with the intensive industrialization of agriculture and the globalization of food. There is therefore a growing interest in the impact of our diet on health, and this interest has focused on several diseases, including neurodegenerative

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disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which are a real global health problem. These diseases are often linked to genetic causes or to exposure to certain neurotoxins. However, they are rarely linked to the constituents of our food and our eating habits. This chapter presents a review of the literature answering the following question. What interaction (prevention and risk) can there be between the constituents of our food and the state of brain health?

Keywords Brain health · Food · Nutrition · Neurodegenerative disorders · Genetic causes · Neurotoxins

1 Introduction

Neurodegenerative disorders are diseases that affect the proper functioning of the nervous system. The most popular worldwide are Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis. The process in question generally consists of a deterioration in the functioning of nerve cells, in particular neurons, up to cell death. The consequences are therefore a progressive and irreversible alteration of nerve functions, which can lead to death. Depending on the regions of the nervous system affected, the disorders can affect motor skills, language, memory, perception, and cognition. Neurodegeneration can affect the central nervous system, the peripheral nervous system, and even the autonomic nervous system. These disorders can be transmitted genetically to the offspring. However, there are so-called idiopathic cases, the exact causes of which are linked to several nongenetic factors, namely exposure to environmental toxins, neuroinflammation, oxidative stress, mitochondrial dysfunction, or the combination of these factors (Mayeux and Stern 2012; Marin et al. 2014; Draoui et al. 2020). Neurodegenerative diseases present significant oxidative stress throughout the body, detected both peripherally and associated with vulnerable regions of the brain affected by the disease, thus causing oxidative damage to neuronal macromolecules via the genesis of reactive oxygen species (Wang et al. 2014). One of the main environmental causes, often overlooked as a risk or preventive factor for mental health, is nutrition. Recent industrialization has profoundly changed human eating behavior by bringing an abundance of ultra-processed foods poor in nutritional elements but rich in sugars and fats (therefore calories), and by reducing access to foods rich in micro- and macronutrients. Eating habits have indeed changed much more in the past 50 years than in previous centuries (Armelagos 2014). There is currently a major paradox in the diet of the general population characterized by overeating (high calorie intake) contrasting with undernutrition in essential nutrients (vitamins, minerals, essential fatty acids), in parallel with a decrease in daily energy needs. It is essential to understand the role played by nutritional habits in causing, preventing, or delaying neurodegenerative diseases. The purpose of this literature review is to synthesize scientific research on the links between diet and brain integrity by looking at the interaction that can be between the constituents of our food and the maintenance of the brain.

2 Clinical Features and Epidemiology

Alzheimer's disease (AD) is the first neurodegenerative disease in the world, and it is the most common form of dementia in humans (Mayeux and Stern 2012; Sosa-Ortiz et al. 2012; Eratne et al. 2018). Based on the 2005 study by an international group of experts affiliated with Alzheimer Disease International in 14 regions of the World Health Organization on epidemiological data acquired in recent years. The results suggested that 24.2 million people were living with dementia at that time, with 4.6 million new cases occurring each year. North America and Western Europe have the highest prevalence of dementia at age 60 (6.4 and 5.4% of the population at age 60), followed by Latin America (4.9%) and China and its neighbors in the Western Pacific (4.0%). Annual incidence rates (per 1000) for these countries have been estimated at 10.5 for North America, 8.8 for Western Europe, 9.2 for Latin America, and 8.0 for China and its neighbors in the western Pacific, increasing exponentially with age in all countries. Compared to Africa, Asia, and Europe, the prevalence of AD appears to be much higher in the United States, which may be related to the methods of determination. Prevalence may be higher among African-American and Hispanic populations living in the United States but lower for Africans in their country of origin (Mayeux and Stern 2012; Eratne et al. 2018). In 2010, approximately 36 million people were affected by AD worldwide, with projections that will reach 66 million by 2030 and 115 million by 2050 (Zouhairi et al. 2019). Although AD is often the term used to describe both the clinical syndrome and the disease entity, some specialists in the field prefer to use Alzheimer's dementia to describe the clinical syndrome associated with a specific neuropathological process defined by two distinctive characteristics: the accumulation of extracellular neuritic plaques composed mainly of 42 amino acids β-amyloids (Aβ1–42), a cleavage product of the amyloid precursor protein, and intracellular collections of neurofibrillary nodes composed of hyperphosphorylated species of tau protein associated with microtubules (Mayeux and Stern 2012).

Parkinson's disease (PD) is the second most common neurodegenerative disorder after AD. The main cardinal motor disorders of this disease are akinesia/bradykinesia, stiffness, and trembling at rest. These disorders are caused by a severe depletion (80–90%) of dopamine in the striatum following a degeneration essentially of the dopaminergic neurons of the substantia nigra. In addition, the clinical description of PD also includes nonmotor symptoms such as anxiety, depression, and apathy. This disease is characterized by the fastest growth in terms of prevalence, disability, and death (6.1 million patients in 2016 compared to 2.5 million patients in 1990), with a prevalence of 0.3% in the general population, 1% for people over 60, and 3% for people of 80 years and over. The incidence rate of PD is 8–18 people/100,000 people/year. The average age of onset of the disease is 60 years, and the average duration of the disease (from diagnosis to death) is 15 years. The majority of epidemiological studies confirm that men have twice the prevalence and incidence rate than women. Except that a recent epidemiological study revealed that the male/female ratio of the age-standardized prevalence rates was similar in 2016. Regarding the mortality rate, the PD left 211,296 deaths in 2016 (Elbaz et al. 2015; Tysnes and Storstein 2017; Ray Dorsey et al. 2018; Draoui et al. 2019, 2020).

In third position comes Charcot disease or amyotrophic lateral sclerosis, which is another very debilitating neurodegenerative disease among the most common neuromuscular diseases (Desport and Maillot 2002; Marin et al. 2011; Erkkinen et al. 2018) with a diagnostic age of 55–70 years and with generally stable incidence in different populations, between 1.5 and 2.5/100,000 person-years. The sex ratio (male/female) is 1.5. Sporadic forms represent 90% of cases, but there are genetic forms, when at least two people are affected in the same family regardless of the degree of kinship (Desport and Maillot 2002; Kiernan et al. 2011; Marin et al. 2011, 2014). Mutations in the superoxide dismutase 1 (SOD1) gene are currently identified. It should be noted that there are sporadic forms also often linked to oxidative stress with considerable and irreversible oxidative damage in the brain (Desport and Couratier 2002; Baillet et al. 2010; Kiernan et al. 2011). Amyotrophic lateral sclerosis is accompanied by progressive degeneration of the motor neurons, varyingly associating a paralysis of the limbs and muscles giving swallowing and salivation disorders. The main forms are the forms starting at the brachial level or at the level of the lower limbs and the bulbar forms. The disease is therefore very debilitating, particularly for autonomy and respiratory function. His prognosis is heavy, with constant worsening during follow-up, leading to death mainly from respiratory failure. Median survival is 24 months after diagnosis with extremes of 6 months to 15 years (Kiernan et al. 2011).

3 Oxidative Stress Causes Neurodegeneration

The term oxidative stress is often questioned in relation to neurodegenerative diseases (Markesbery 1999; Baillet et al. 2010; Wang et al. 2014). It is defined as a disturbance of the balance between the production of reactive oxygen species (free radicals) and antioxidant molecules, thus causing tissue damage. Free radicals are formed in large quantities as a result of many biochemical processes and, in some cases, deliberately, as inactivated neutrophils (Betteridge 2000). Significant oxidative stress throughout the body is present in patients with neurodegenerative diseases, detected at the periphery and associated with very vulnerable regions of the brain affected by the disease. Abundant evidence not only demonstrates the full spectrum of oxidative damage to neuronal macromolecules but also reveals the occurrence of oxidative events at the onset of the disease and before the onset of pathology, which support an important role of oxidative stress in this pathology. Oxidative damage is found at levels that considerably exceed those of the elderly controls, which suggests the implication of one or more amplifying factors, notably lifestyle among others and the diet (Markesbery 1999). The intense cellular oxidative stress causes alterations of the detoxification systems and of the intracellular redox potential, the depolymerization of tubulin, a strong decrease in glucose capture, but especially the peroxidation of cellular macromolecules among which lipids, nucleic acids, and mitochondrial alterations, the latter producing superoxide radicals, induce a significant decrease in intracellular ATP levels. The main consequences of this, on the one hand, alter the vesicular storage of neurotransmitters, which causes a cytosolic increase in the neurotransmitter generating a reaction cascade that aims at the release of reactive oxygen species and other, on the other hand, to disturb the membrane polarization, which induces indirect excitotoxicity accompanied by a deleterious deregulation of calcium homeostasis (Lambeng et al. 2002).

4 Eating Habits and Central Nervous System

Currently, it is universally accepted that there is a so-called oxidative diet and an antioxidative diet (Morelle-Lauzanne 2006). Nutritional epidemiology is more concerned with the study of whole diets rather than with individual nutritional elements. This more global approach takes into account the interactions between different foods. In 1995, a Mediterranean Dietary Score (MDS) was even created to more objectively assess the level of adherence to this diet. Thus, according to several prospective studies, it significantly reduces overall mortality and the risk of neurodegenerative diseases, notably AD and PD (Sofi et al. 2008, 2010; Wade et al. 2018). The Mediterranean diet is today one of the only diets recommended for the prevention of frequent chronic diseases such as metabolic, cardiovascular, neurodegenerative, and cancer pathologies. It was admitted that the Parkinsonian patients adhere less than the controls to a Mediterranean type diet (Alcalay et al. 2012). Historically, the Mediterranean diet was defined by the type of diet of people living in the olive-growing regions around the Mediterranean basin (mainly Greece, Southern Italy, and Spain) before the 1960s. The Mediterranean is characterized by an important consumption in fruits, vegetables, whole cereals, nuts, seeds and legumes, a moderate consumption in white meats, lean fish, and dairy products, a low consumption of red meats, sweet products, and processed products, and finally an almost exclusive use of olive oil for cooking. Alcohol consumption is traditionally moderate during meals and consists exclusively of red wine (Willett et al. 1995). Fat intake is high, but with a high monounsaturated/saturated fat ratio due to the use of olive oil and nuts. It has been shown to provide high intakes of vitamins, polyunsaturated fatty acids omega-3 and omega-6, and monounsaturated amino acids and minerals. The contributions of these nutrients probably explain the positive effects of the Mediterranean diet recognized worldwide. Consumption of whole grains and fiber has also been significantly associated with a reduced risk of developing chronic diseases (Huang et al. 2015). The Mediterranean diet is close to those qualified as “healthy” or “careful,” but unlike the latter, it encourages high fat intake, but of good nutritional quality. Diet therefore has a vital role in the prevention of chronic diseases, and in particular in the maintenance of good brain health.

4.1 Vitamins

The antioxidant vitamins are known to protect cells from oxidative damage by neutralizing the effects of reactive oxygen species (Miyake et al. 2011). Most fruits and vegetables are sources of antioxidants, including vitamins A, B, C, D, and E, which are present at low levels in some patients with neurodegenerative diseases (de Lau and Breteler 2006; Murakami et al. 2010; Li and Shen 2012; Seidl et al. 2014; Agim and Cannon 2015; Ascherio and Schwarzschild 2016; Park and Ellis 2020). To use the energy provided by carbohydrates, the nervous system needs vitamin B1, so this vitamin modulates cognitive performance. It is found in particular in Brewer's yeast, wheat germ, and sunflower seeds. Vitamin B9 or folic acid, found in particular in asparagus, spinach, lentils, oranges, and certain yeasts, protects the brain during its development and promotes memory. Vitamins B6 and B12, among others, are directly involved in the synthesis of certain neurotransmitters. Vitamin B6 is found in many animal and vegetable foods. Vitamin B12 is found mainly in the liver and seafood. Increasing the intake of B vitamins (B6, B12) involved in the regulation of homocysteine metabolism could decrease the risk of PD and AD by decreasing plasma homocysteine (Murakami et al. 2010; Mayeux and Stern 2012; Agim and Cannon 2015). α-tocopherol, one of the forms of vitamin E (found in vegetable oils, nuts, green vegetables, and some cereals), is actively used by the brain to protect the nervous membranes, thereby reducing the risk of neurodegeneration (Yang et al. 2017). Li and Shen 2012 suggest that vitamin E has the most pronounced protective effects in the case of AD (Li and Shen 2012). Vitamin C has a major role in modulating glutamatergic, cholinergic, dopaminergic, and GABA-ergic neurotransmissions, as well as in neuronal differentiation, maturation, and survival processes. It also has powerful antioxidant properties that are beneficial in combating imbalances in cerebral oxidative stress (Luchsinger et al. 2003; Li and Shen 2012; Seidl et al. 2014).

4.2 Trace and Essential Elements

Trace elements are mineral salts necessary in very small quantities and irreplaceable for the homeostasis of the organism. The effect of a trace element depends on the intake dose. When the trace element is said to be essential, a deficiency or on the contrary an excessive intake can lead to serious disorders (Calderón Guzmán et al. 2019; Mezzaroba et al. 2019). Iron is necessary for oxygenation and energy production in the brain parenchyma (via cytochromes oxidases) and for the synthesis of neurotransmitters and myelin. It is mainly found in animal products (Ward et al. 2014). Magnesium, zinc, and iodine also have an essential function in the good functioning of the brain. Magnesium is found, among others, in seafood, cocoa, whole grains, and dried fruits; zinc in large quantities in oysters, crab, and beef; and iodine in fish, seafood, and algae (Koning et al. 2019; Mezzaroba et al. 2019;

Pinto et al. 2020). Copper is necessary for the proper functioning of the enzyme (Cu, Zn–SOD) and of the cytochrome c oxidase (Desport and Couratier 2002). The addition of magnesium, for example, as a dietary supplement, has been shown to be beneficial, and this by inhibiting the spontaneous aggregation of α-synuclein responsible for neurodegeneration in the case of PD (Agim and Cannon 2015). On the other hand, high iron levels participate in the formation of $OH^{•-}$ radicals in significant quantity at the level of senile plaques and neurofibrillary aggregates characteristic of neurodegeneration, particularly AD (Desport and Couratier 2002). Excessive levels of Zn, for example, suppress the absorption of Cu and Fe, thereby promoting production of reactive oxygen species in the mitochondria, disrupting the activities of metabolic enzymes, and activating apoptotic processes in neurons (Mezzaroba et al. 2019). Copper, reduced from Cu^{2+} to Cu^{+} under the action of the precursor of the β-amyloid protein, also catalyzes the formation of free radicals, particularly $OH^{•-}$ (Desport and Couratier 2002).

4.3 Polyphenols

Polyphenols are a class of molecules abundant in plants used as powerful spices. They are very diversified secondary metabolites classified into flavonoids, phenolic acid, and its derivatives, lignans, and stilbenes with more than 8000 molecules referenced so far. Growing evidence from epidemiological studies, in vivo and in vitro studies, as well as clinical trials and meta-analyses suggests that a high intake of polyphenols, widely present in the culinary arts of many civilization, particularly the Mediterranean diet, can reduce the risk of chronic diseases and improve human health (Fiorentini et al. 2015; Fenga et al. 2016).

Curcumin

Previous studies mentioned that curcumin-I and curcumin-III restore neurotransmitter levels, especially dopamine, noradrenaline, and serotonin with a significant protection against neuronal disruption induced by acute and chronic lead exposure (Benammi et al. 2014; Tamegart et al. 2019). In addition, curcumin-I has a neuroprotective effect in two experimental models of copper exposure (Abbaoui and Gamrani 2018, 2019; Abbaoui et al. 2019). In the olfactory bulbectomy model of depression, the neuroprotective efficacy of curcumin has been studied with neuromodulation of the central monoaminergic neurotransmitter systems (Xu et al. 2005). Curcumin-I is implicated in neuroprotection against acute and chronic aluminum exposure (Laabbar et al. 2014, 2019).

Saffron

It (*Crocus sativus* L.) contains more than 150 chemical components such as picrocrocin, safranal, and crocin (Srivastava et al. 2010; Sarfarazi et al. 2019). Crocin administration (15 and 30 mg/kg) protects against memory deficits in rats (Pitsikas et al., 2007). Researchers have revealed that crocetin, an important food ingredient in India, is useful in preventing parkinsonism and has a potential therapeutic effect against this devastating neurological disorder (Ahmad et al. 2005). In addition, the aqueous extract of *Crocus sativus* L. restores dopaminergic and noradrenergic damages with an obvious neuroprotective effect after acute lead exposure (Tamegart et al. 2018).

Other Molecules
Several bioactive molecules are known by their effect against neurodegenerative diseases such as ferulic acid, vanillic acid, apigenin, and diosmetin. In a mouse model of Alzheimer's disease, it was suggested that ferulic acid could be useful for the prevention of neurodegeneration after chronic oral administration (Yan et al. 2013). It has been mentioned that vanillic acid is a natural compound used as a neuroprotective agent against Alzheimer's disease by attenuating oxidant stress and cognitive impairment in mice (Amin et al. 2017).

4.4 Alcohol

Studies on chronic alcoholism effect on the central nervous system have demonstrated the neurotoxicity of alcohol. Chronic alcoholism may likely lead to brain injury due to several causes including poor nutrition, liver disease, and head trauma. Further, up to 50–75% of long-term alcoholics may suffer from permanent cognitive impairments, placing chronic alcoholism as the second leading cause of dementia, accounting for approximately 10% of the cases, after AD (Crews et al. 1996).

Several studies in both humans and rodents had reported that chronic alcohol consumption induces several changes in the structure of the adult brain. In human computed tomography and magnetic resonance imaging, studies had demonstrated that longer alcoholism produces swelling of the cerebral ventricles and sulci, which reflects a decreased brain mass. Additionally, reduction in total brain weight was reported in earlier researches on postmortem brain tissue (Sutherland et al. 2014). Loss of brain mass is explained by a selective loss of neurons and resulting loss of myelin sheath white matter, reduction in the brain parenchyma, dendritic simplification, and reduction of synaptic complexity in specific brain regions (locus coeruleus and raphe nuclei and anterior superior vermis of the cerebellum) of alcoholics. Ethanol neurotoxicity may have several modes of action, comprising

- Glutamate excitotoxicity.

Several studies had highlighted the involvement of *N*-methyl-D-aspartic acid (NMDA)- glutamate receptors in tolerance and dependence as well as ethanol-induced brain impairments. Supersensitive glutamate-NMDA response appears to be involved in CNS hyperexcitability, even if a diminution in GABA-mediated inhibition could participate too (Crews et al. 1996). In fact, in the human hippocampus of alcoholics, scientists had reported an increment in [^{3}H] glutamate binding, which is consistent with increased glutamate receptor density and sensitivity (Michaelis et al. 1990). Excessive stimulation of NMDA-glutamate receptors triggers a process in neurons that leads to neuronal death.

- Oxidative stress.

Experimental studies on the ethanol effects on cellular oxidation had shown chronic ethanol-induced increase in oxidant enzyme levels such as CYP2E1, an ethanol-inducible form of cytochrome P450, and a potent generator of oxidative radicals (Montoliu et al. 1994). Moreover, chronic ethanol-induced increases in oxidases have been related to increased lipid peroxidation and reactive oxygen radicals in the brain. It has been shown that a single dose of ethanol results in both the increase of lipid hydroperoxide levels and decreases in glutathione levels in rat brain homogenates (Haorah et al. 2008). Thus, ethanol-induced neurotoxicity may be linked to induction of oxidative stress.

4.5 Fatty Acids Neurotoxicity

Fatty acids are an important class of lipids and the essential monomeric constituent of all lipid types. Fatty acid oxidation is one of the most important contributors to reactive oxygen species production. Even if fatty acids are not the main substrate for energy production in the cell, their β-oxidation generates a considerable quantity of reactive oxygen species. Consecutively, these promote several harmful oxidative effects including lipid peroxidation, protein oxidation, DNA damage, and apoptosis. As neurons are not effectively equipped to deal with oxidative stress, these harmful effects are multiplied, contributing to neurodegeneration (Tracey et al. 2018).

Several studies had reported an increased lipid peroxidation in AD, supporting a role for oxidative impairment in this disorder (Moses et al. 2006). Thus, recent researches had shown an enhancement in the levels of 4-hydroxynonenal and acrolein (Williams et al. 2006) in the brain tissue of patients with mild cognitive alteration and early AD, suggesting that lipid peroxidation takes place at the beginning of AD pathogenesis (Williams et al. 2006). Considered as the most powerful electrophile of all unsaturated aldehydes, α,β, acrolein interacts with DNA bases to produce cyclic adducts, the primary exocyclic adduct being acrolein-deoxyguanosine. Elevated levels of acrolein-deoxyguanosine adducts have been shown in the brain tissue of patients with AD (Liu et al. 2005). ROS may also play a potential role in amyloid deposition in AD as oxidative conditions cause protein cross-linking and peptide aggregation of Aβ, and also contribute to tau protein aggregation (Mariani et al. 2005).

Oxidative stress induced by free radical production and lipid peroxidation plays a significant role in the pathogenesis of PD. In fact, several markers of lipid peroxidation have been shown be highly increased in brain regions of PD, such as the concentration of polyunsaturated fatty acids in substantia nigra being decreased, while that of malondialdehyde, a marker of lipid oxidation, is increased. More evidence of lipid oxidation in PD is given by the demonstration of an increase in 4-hydroxy-2-nonenal, alipophilic membrane-bound peroxidation product of arachidonic acid. This indicates that the pathogenesis of PD involves lipid peroxidation that accelerates dopamine metabolism (Maxfield and Tabas 2005; Larsen et al. 2007).

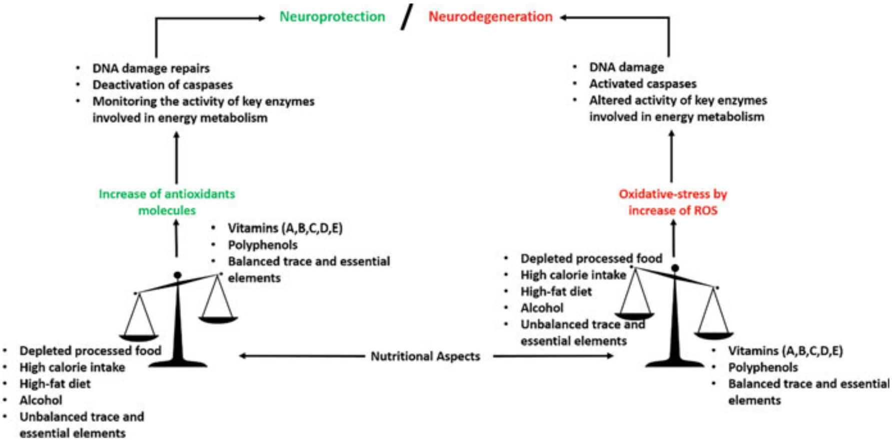

Fig. 1 Schematic representation of the interactions between nutritional aspects and the central nervous system

5 Conclusion

Food should be considered universally as a potential risk factor or protective factor for mental health (Fig. 1). The chemical composition of our food has a significant influence on the oxidative state in the brain. Favoring a so-called antioxidant diet results in neuroprotection. Food antioxidants have multiple effects and target several specific processes. Vitamins A, B, C, E, and polyphenols like curcumin and saffron are able to interact directly with ROS and stop oxidative chain reactions. This suggests that a balanced diet can be used as a nonpharmacology prevention and treatment for the maintenance of mental health.

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Acrylamide, the Unnatural Compound: Exposure and Toxicity on Humans and Animals

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Abstract Since the 1950s, the production and use of acrylamide (Acry) have gained interest around the globe in various fields. This compound is not found naturally in food. Nevertheless, it is widely abundant. Its abundance is due to domestic cooking processes such as frying and routing or industrial food processing at temperatures above 120 °C.

Many health issues are a result of acrylamide toxicity, including the immunotoxic, hepatotoxic, neurotoxic, genotoxic, carcinogenic, teratogenic, as an endocrine disruptor and agent, which induces oxidative stress at the tissue level. The nervous system is reportedly the main target of that vinyl compound, which results in several manifestations of neurotoxicity such as ataxia, peripheral and central

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neuropathy, and muscle weakness. The toxic effect of acrylamide is moreover extended to prenatal and postnatal periods causing several disorders on both the mother and fetus.

As a contribution to the understanding of nutritional behavior's influence on human health, this chapter represents a review of the most pertinent advancement on the subject. Thus, it represents a revision of its influence on human health.

Keywords Acrylamide · Toxicity · Human health

1 Introduction

Since the 1950s, the production and use of acrylamide (Acry) have gained interest around the globe in various fields. Acrylamide is synthesized as a monomer by the hydration of acrylonitrile with either inorganic catalysts or biocatalysts (Klein 2007). It is predominantly used because of the easiness of Acrys' handling in different sectors such as in the construction of plastic food packaging.

Acry is not found naturally in food. Nevertheless, its abundance is due to domestic cooking processes such as frying and routing or industrial processing at temperatures above 120 °C (Weiss 2002). Such formation is only possible through the Maillard reaction, which takes place between reducing sugars like glucose, fructose, and amino acids such as asparagine (Klein 2007; Al-Gholam et al. 2016; Gökmen 2016; Erdemli et al. 2016).

The toxic nature of Acry was disclosed earlier through multiple studies, epidemiological studies carried out in a professional environment, and on animals at different doses and variable exposure routes mainly oral, intraperitoneal, and by inhalation. Many health issues were revealed, including the immunotoxic, hepatotoxic, neurotoxic, genotoxic, carcinogenic, teratogenic, as an endocrine disruptor and agent that induces oxidative stress at the tissue level (Al-Gholam et al. 2016; Belhadj 2018). Several in vivo and in vitro studies give more attention to investigating the Acrys' harmful effects at different scales: clinical, biochemical, molecular, as well as anatomopathological. The point has even been made to modernize analytical methods allowing its detection and its reduction in foodstuffs (Biedermann et al. 2002; Al-Gholam et al. 2016; Belhadj 2018). Moreover, the nervous system is reportedly the main target of that vinyl compound in humans, which results in several manifestations of neurotoxicity such as ataxia, peripheral and central neuropathy, and muscle weakness (Krishna et al. 2015).

As a contribution to the understanding of nutritional behavior's influence on human health, this chapter represents a review of the most pertinent advancement on the subject. Thus, it first shed light on the frequent sources of contamination and then represents a revision of its influence on human health.

In humans, the toxicity of Acry following sub-chronic to chronic exposure leads to clinical manifestations similar to its acute toxicity, such as ataxia, locomotion disorders that can go as far as paralysis, and/or weakness of the muscles. Skeletal muscles, numbness in the limbs, altered sensation, weight loss, and nystagmus as well as skin irritation, these signs have been observed in people exposed to Acry in the workplace (Klein 2007; Pennisi et al. 2013; INRS 2019).

For this, researchers suggest that the nervous system is the main site of Acry toxicity in humans (Gold et al. 2004; Klein 2007; Hammad et al. 2013).

2 General Description and Use

Acrylamide is among the multitude of toxic products known to date (Brisson-Gauthier, 2012). This organic compound, also called 2-propenamide (C3H5NO), acrylic amide, or ethylene carboxamide (Carrara 2018), is identified and characterized by the chemical formulas (raw, semi-developed) (Fig. 1).

Acry is widely used in industries and is commercially available. In 1955, more than 99.9% of its monomeric form was used in the manufacture of high molecular weight polymer, the polyacrylamide in the form of the three-dimensional network by a radical polymerization process that takes place between Acry and bis-acrylamide (N, N′ methylene-bis- acrylamide). This acts as a bridging agent, and its quantity determines the rate of cross-linking and porosity of this polymer in the presence of free radicals generated by reactive initiators used in aqueous solution (Friedman and Mottram 2005; Klein 2007; Carrara 2018).

3 Acrylamide in Food

3.1 Discovery of Acrylamide in Food

In 1998, analyses indicated that Acry can form in animal foods and cooked hamburgers (Tareke et al. 2000; Eriksson 2005). On 9 January 2001, Analy Cen and the Dept of Environmental Chemistry (ACDEC) detected high levels of Acry up to (700 μg/kg) in French fries (Eriksson 2005). In April 2002, a group of researchers from the University of Stockholm and the Swedish National Food Agency (SNFA) proved that cooking at a high temperature above (<120 °C) either by frying or by routing of some foods consumed daily (particularly foods rich in carbohydrates such as cereals, fries, crisps, pastry, and sliced bread) could cause the formation of Acry

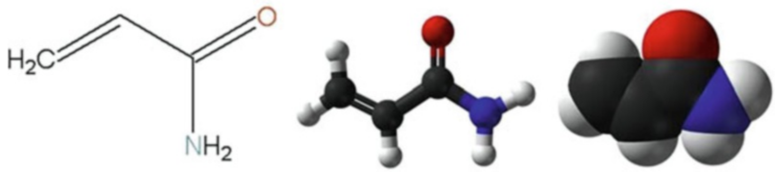

Fig. 1 The 2D and 3D chemical formulas of Acylamide (Belhadj 2018)

compounds in relatively high and unexpected quantities (Friedman and Mottram 2005; Klein 2007; Government of Canada 2009; ATSDR 2012; Carrara 2018).

After this discovery, various researches were undertaken to explain its neogenesis in food, and finally, they established that it was formed through the Maillard reaction (MR) (WHO 2003; Klein 2007), then other research concluded that Acry can also be neoformed via several reactions following the intervention of free amino acids, proteins, lipids, and by dehydration, decarboxylation of certain common organic acids: malic acid, lactic acid, and citric acid, or other minor components in cooked food (FAO/WHO and Health Implications of Acrylamide in Food 2002).

3.2 Acrylamide Formation in Food and the Maillard's Reaction

The Maillard's reaction is a nonenzymatic, nonoxidative browning. It is a complex reaction that occurs between free amino and carbonyl compounds (reducing carbohydrates) as a result of cooking food at high temperatures, drying of food, or storage (Fig. 2) (Eriksson 2005). This reaction is also known as glycation or glycoxidation reaction at the level of biological systems that can occur in vivo at 37 °C (Maillard reaction at a physiological medium). This takes place between proteins and

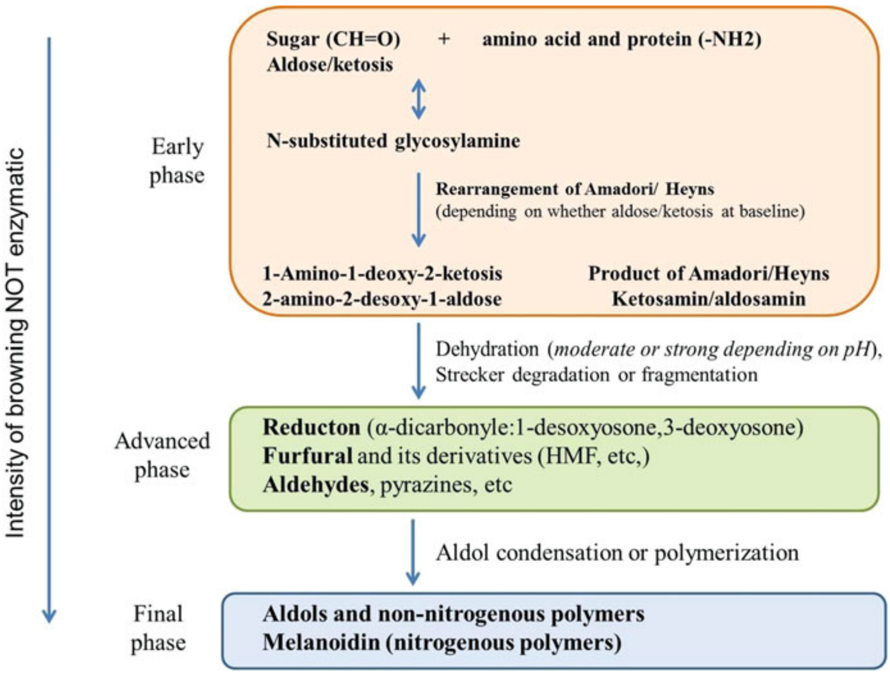

Fig. 2 General diagram of the Maillard reaction (Cladière and Camel 2017)

accumulated or free sugars such as glycated hemoglobin A1C (HbA1C) and albumin fucosylation by acting on their functioning.

3.3 Acrylamide and Food Security

The Swedish National Food Administration and the University of Stockholm jointly raised the alarm on the presence of Acry in certain foods (Swedish National Food Administration 2002). The contamination of cooked food by Acry needs indeed to be controlled. This was the objective of various commissions, agencies, and world organizations in assessing this health risk. In the United States, the Food and Drug Administration (FDA) in collaboration with the European Food Authorities (EFSA) has established an online database accessible to the public by exposing the concentration of Acry in food. In parallel, organizations founded databases on Acry's reference levels in food (CAST 2006; Wenzl and Anklam 2007) with regularly updated information (CAST 2006; Klein 2007). Foods with the highest concentrations of Acry include potato products (such as French fries, crisps), cereals, cookies, biscuits, cakes, bread, as well as roasted coffee (Taeymans et al. 2004).

Dietary exposure to Acry has indeed taken a significant part of the total exposure of the population because the products contaminated by this agent are regularly consumed in fairly large quantities daily (FAO/WHO 2002; Lineback et al. 2012). These foods contribute to more than 80% of the doses of Acry ingested (Dybing et al. 2005). Thus, the daily doses have been estimated at 0.3–0.8 μg/kg of body weight for the general population by surveys based on food consumption. However, these doses are threefold in children compared to adults (FAO/WHO 2002), which is probably due to their low body weights as well as the increased consumption of foods rich in Acry (crisps and cookies) (Dybing et al. 2005; Wilson et al., 2006). These estimates vary from country to country, which may be related to eating habits as well as the mode of food preparations (Dybing et al. 2005). Some cosmetic products and plastic food packaging containing free Acry may also present another source of exposure to this agent through the skin or ingestion of small amounts (FAO/WHO 2002; Santacana 2016).

4 Toxicity of Acrylamide

4.1 Acute Toxicity

Depending on the route of exposition, either cutaneous, through inhalation, or swallowed, the Acry can irritate skin, eyes, and respiratory tract, as it may cause digestive disorders such as nausea and vomiting. Besides, it may set off central and even peripheral neuropathy that, reportedly according to experimental and epidemiological studies, is manifested by reduced motricity coordination, numbness, tremors, ataxia, asthenia, paresthesia, seizures, and confusion, as well as memory loss, hallucinations, and weight loss, all of which are reversible in a few days (Kopp 2009).

Experimentally, a study shows that signs of peripheral neuropathy may appear following either oral administration of five daily doses of 45 or 75 mg/kg bw/day in rats or by inhalation. The rats exposed to 15.6 mg/m^3 Acry (6 h/day, 5 day/week, 12 exposures in total over 16 days) suffer from loss of balance and motor incoordination, but effects are neither reported in dogs nor guinea pigs exposed the same way (INRS 2019). It is worth mentioning that the lethal dose of Acry 50 (LD50) in rodents was estimated to be 107–203 mg/kg (EFSA 2015; Belhadj 2018).

In humans, several cases of acute intoxication in the workplace and through the skin have shown signs such as skin rash, sweating, desquamation, and acne-like dermatitis of the palmar surface, which symptoms constantly precede the neurological damage (INRS 2019). Other symptoms were observed in a 23-year-old woman who has had depression previously. After ingesting 18 g of acrylic crystals, the subject presented after 5 h hallucinations, hypotension, and gastrointestinal bleeding (despite repeatedly going through gastric washes). Moreover, respiratory distress syndrome and hepatotoxicity took place since the third day after ingestion, and symptoms of peripheral neuropathy persisted for a couple of months (Kumar et al. 2018).

4.2 Subchronic and Chronic Toxicity

In humans, subchronic to chronic exposure to Acry leads to clinical manifestations similar to acute toxicity. To be mentioned, some relevant examples are locomotor disturbances that can lead to paralysis, skeletal muscle weakness, numbness of the limbs, altered sensation, weight loss, and nystagmus as well as skin irritation; these signs have been observed in individuals exposed to Acry in the workplace (Klein 2007; Pennisi et al. 2013; INRS 2019). To this end, researchers suggest that the nervous system is the main target site of Acry toxicity in humans (Gold et al. 2004; Klein 2007; Hammad et al. 2013). For animals, however, in addition to its predominant neurotoxic effect, several other effects have been documented depending on the dose and the time of exposure. More details are presented hereafter.

5 Effects on the Body Weight

Acry reportedly induces body weight loss according to various studies on laboratory animals exposed to different doses at a variety of periods of exposure (Gipon et al. 1977; ATSDR 2012; Abdullah 2019).

6 Gastrointestinal Effects

The gastrointestinal tract is one of the most exposed tissues to high concentrations of Acry due to the high absorbability of this tissue (Zödl et al. 2007). Consequently, Acry affects the integrity and hemostasis of the gastrointestinal barrier by inducing histopathological changes, leading to erosion of the gastric mucosa associated with inflammation and hemorrhage (El- Mehi and El-Sherif 2015).

In the small intestine, Acry alters the histological structure, renewal, and innervation of the intestinal epithelium (Dobrowolski et al. 2012). Exposure during gestation in guinea pigs showed that Acry caused adverse effects on the small intestine in litters characterized by decreased cadherin expression in the epithelium, decreased number of crypts in the duodenum and jejunum, narrowing of the submucosa and muscular, in addition to hypertrophy of the myenteric plexus (Tomaszewska et al. 2014). Acry exposure causes a shortening or even degeneration of ileum villi affecting intestinal absorption, reduces the expression of occludin and claudin, and increases the intestinal content of lipopolysaccharides affecting the microbiota (Tan et al. 2019).

In the colon, Acry disrupts the homeostasis of the colonic mucosa by modifying the synthesis and secretion of mucus, a double layer constituting a primary defense barrier of the intestinal wall. This takes place especially because of generating an imbalance between the proliferation and differentiation of calciform cells (responsible for mucus secretion) in young rats (Koledin et al. 2016), and similarly leads to degeneration of Lieberkühn crypts and epithelial lesions (Gedik et al. 2018).

Although the exact mechanism of this effect is still poorly understood, the available data suggest that oxidative stress is the main cause of these alterations (Sadek 2012; El-Mehi et El-Sherif 2015; Erdemli et al. 2015; Koledin et al. 2016; Chen et al. 2016; Gedik et al. 2018).

7 Cardiovascular Effects

Acry affects the physiology of the cardiomyocytes by altering their integrity, morphology, and ionic balance. This desynchronizes its contraction and generates arrhythmias, according to many studies that have been established in vitro at various doses for various durations of exposure. Additionally, Acry decreases the sensitivity of smooth muscles to neuro-mediators such as acetylcholine, subsequently modifying its contraction (Walters et al. 2014). Acry also induces depletion of the antioxidant systems at the cardiac level (generation of free radicals), inflammation, and disturbance of circulating HDL and LDL levels through its co administration with aluminum (Ghorbel et al. 2015). Histologically, Acry causes hemorrhages between myocardial muscle fibers associated with degeneration and loss of striation (Mansour et al. 2008).

8 Hematological Effects

Acry causes hematological disturbance and even anemia in rats (Sharma and Jain 2008; El-Kholy et al. 2012). It damages the erythrocyte membranes, in a lipid and protein peroxidation process, through generating micro-nucleated deformed and aggregated red blood cells. The appearance of anemia is a consequence of the formation of hemoglobin adducts and a decrease in the index of erythrocyte deformability. All these signs will slightly increase viscosity, which results in a decrease in blood fluidity, leading to cardiovascular disease (Arıhan et al. 2011).

9 Hepatotoxic Effects

The hepatotoxicity of Acry has been reported after acute intoxication in a woman who ingested 18 g of Acry, although there is no data to address this effect in humans (Kumar et al. 2018). In animal models, several studies agreed that Acry induces oxidative stress in the liver manifested by an alteration of antioxidant status and an increase in the products of protein oxidation and lipid peroxidation (Ghorbel et al. 2017). Histological and tissue lesions are observed in the liver such as hemorrhage, inflammation, necrosis, degeneration, steatosis, and congestion of blood vessels (centrilobular vein and sinusoid capillaries) (Mansour et al. 2008; Rawi et al. 2012; Mahmood et al. 2015; Gedik et al. 2017; Shrivastava et al. 2018).

Elevated plasma levels of liver enzymes such as alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), and alkaline phosphatase (ALP), as well as increased triglycerides and cholesterol levels, have also been reported. On the other hand, Acry decreases total protein and albumin levels, which may be due to delayed protein synthesis or a change in metabolism (Rawi et al. 2012; El-Kholy et al. 2012; Soliman 2013; Mahmood et al. 2015; Ghorbel et al. 2017).

10 The Effects on the Immune System

The effects of Acry on the immune system, particularly on cell-mediated immunity, are manifested by a decrease in the percentage of T-cells and the number of natural killer cells (NK). Moreover, it leads to atrophy of the primary and secondary lymphoid organs, especially the spleen, thymus, and lymph nodes (Zaidi et al. 1994; Mansour et al. 2008; Yener et al. 2013; Zamani et al. 2018). Additionally, in the spleen, Acry causes oxidative stress through GSH depletion and increased lipid peroxidation as well as activation of apoptosis and inhibition of proliferation (Jin et al. 2014; Zamani et al. 2018).

For humoral-mediated immunity, Acry decreases immunoglobulin (IgG and IgM) levels (Soliman 2013; Khudiar and Hussein 2017) and also inhibits the production of interleukin-6 (IL-6) (Jin et al. 2014).

11 The Effects on Kidney

Kidneys are the main organ where Acry is excreted. In fact, in animals, the renal effects are explained both by glomerular and tubular lesions. The glomerular lesion causes the appearance of glomerulonephritis with proteinuria affecting plasma filtration (Jamshidi and Zahedi 2015). However, tubular lesions are manifested with renal tubular epithelial cell degeneration and necrosis, loss of the brush border and cell vacuolation, and inflammation (Mansour et al. 2008; Rawi et al. 2012; Mahmood et al. 2015; Rajeh and Al-Dhaheri 2017; Shrivastava et al. 2018). One study shows that administration of Acry during gestation induces oxidative stress in the renal tissues of rabbits and their fetuses, resulting in tissue damage and changes in the Bowman's capsule (Erdemli et al. 2016).

12 Reproductive Effects

12.1 Effects on Reproductive Parameters

Numerous experiments using different doses and durations of exposure have demonstrated the reprotoxic effect of Acry in animals. Nevertheless, in humans, no effects have been observed or identified (Kumar et al. 2018; INRS 2019).

Acry reduces fertility in rodents (Sakamoto and Hashimoto 1986; Chapin et al. 1995; Tyl et al. 2000; Wang et al. 2010; AlKarim et al. 2015; Kumar et al. 2018). In these rodents' male rats, impaired fertility involves a decrease in sperm count associated with abnormal morphology and changes in motility (Sakamoto and Hashimoto 1986; Tyl and Friedman 2003; Ma et al. 2011), testicular atrophy, and histopathological lesions in the seminiferous tubules such as vacuolations, inflammation, and germ cell degeneration (Hashimoto et al. 1981; Alkarim et al. 2015), as well as decreased testosterone levels (Yang et al. 2005; Camacho et al. 2012). Similarly, exposure to Acry in rats (at 100 ppm) disrupts mating performance, erectile processes, and sperm transport (Zenick et al. 1986; Semla et al. 2017).

The involvement of oxidative stress in Acry reprotoxicity has also been described at the level of Leydig and Sertoli cells, where decreased cell viability and an increase in reactive oxygen species (ROS), in addition to induction of apoptosis, have been established by increased expression of apoptotic genes (Yilmaz et al. 2017; Matoso et al. 2019).

In female mice, Acry leads to ovarian atrophy, alters oocyte quality (Duan et al. 2015), decreases corpus luteum count, and lowers progesterone levels. Similarly, it reduces in vitro the viability of granulosa cells in a dose-dependent manner (Wei et al. 2014). Moreover, it impedes oocyte maturation by disrupting cell division, reducing the meiotic spindle, and an increase in chromosomal breakage (Aras et al. 2017).

Prenatal exposure in guinea pigs reduces the number of ovarian follicles by inducing follicular atresia mediated by oocyte apoptosis, which may be associated with the destruction of the vimentin filaments (Hułas-Stasiak et al. 2013).

In another study conducted by Alkarim et al. (2015), it was shown that a low dose of Acry causes degenerative changes in the zona pellucida, granulosa cells, and oocytes in female rats and that Acry affects oocyte quality through its effects on cytoskeletal integrity, ROS generation, apoptosis induction, and epigenetic changes (Duan et al. 2015).

Besides, it has also been shown in vitro that the epoxide Glyc component is toxic to germ cells where it leads to degeneration of the totality of oocytes (Aras et al. 2017). Such toxicity is associated with apoptosis following the generation of ROS and increasing lipid peroxidation in Leydig cells when cultured with Glyc, leading to a decrease in progesterone synthesis (Li et al. 2016; Matoso et al. 2019).

13 Effects on Pregnant Females and Offspring

A large number of studies in rodents have pointed out that exposure to Acry during gestation results in increased fetal mortality and preimplantation loss. This may be due in part to male impotence (erectile inhibition) or quantitative and qualitative sperm abnormalities (Sublet et al. 1989; Klein 2007; Alkarim et al. 2015). Acry decreased fetal weight growth at birth as well, which can be considered as a side effect of maternal toxicity; similarly, Acry decreases the number of pregnant females (Sakamoto and Hashimoto 1986; Chapin et al. 1995; Tyl et al. 2000; Tyl and Friedman 2003).

Acry has also been reported to inhibit placenta development by reducing the expression of placental genes and labyrinthine vessels, as well as by suppressing proliferation and inducing apoptosis (Yu et al. 2019).

14 Genotoxicity and Mutagenicity

14.1 Carcinogenic Effects

In 1994, the International Agency for Research on Cancer (IARC) classified Acry as probably carcinogenic to humans (IARC 1994). This assessment was based primarily on the Acry that is known to be a genotoxic agent (mutagenic and clastogenic) to somatic and germ cells in vivo and in vitro. It causes several genetic effects such as chromosomal aberrations, micronucleus formation, sister chromatid exchanges, unscheduled DNA synthesis, and dominant lethal mutations (FAO/WHO 2002; Wang et al. 2010; Beland et al. 2015), and germ cells are more sensitive to these effects (Tyl and Friedman 2003).

However, several in vitro and in vivo studies have shown this genotoxicity to be attributed to its metabolite Glyc thanks to its electrophilic properties toward DNA. Compared to that, the Acry's reactivity to DNA appears to be very low (Segerbäck et al. 1995; Gamboa da Costa et al. 2003; Twaddle et al. 2004; Doerge et al., 2005a, b, c; Ghanayem et al. 2005; Tareke et al. 2006; Von Tungeln et al. 2009; Zeiger et al. 2009). However, at high doses, its genotoxicity becomes important (Yang et al. 2005; Manjanatha et al. 2006), whereas its epoxide acts at lower doses and causes mutations (Besaratinia and Pfeifer 2003, 2004).

Glyc is also genotoxic to human cells in vitro, such that when tested on human whole blood for 4 h, it induces DNA damage in lymphocytes (Baum et al. 2005), and on epithelial cells, it induces micronuclei, inhibits cell proliferation, and decreases cell viability (Bandarra et al. 2013). Knowledge of the carcinogenicity of Acry was founded on studies in rodents since the 1980s (Klein 2007). However, most studies conducted on humans have not provided conclusive data on the association of human cancers and exposure to Acry (Beland et al. 2013, 2015; Zhivagui et al. 2019).

The carcinogenicity of this compound has been examined by several investigators, who have observed that chronic exposure (for 2 years) to high-dose Acry in rats causes an increase in tumors of the testes and thyroid, uterus and mammary glands, and even tumors of the central nervous system (Johnson et al. 1986; Friedman et al. 1995; Maronpot et al. 2015). Compared to mice, it induces lung tumors, liver tumors, and has also been classified as a skin carcinogenesis initiator (Robinson et al. 1986; Bull et al. 1984; Von Tungeln et al. 2012), and prenatal exposure induces tumors in the small intestine in a dose-dependent manner in neonatal mice (Olstorn et al. 2007).

The mechanism of this carcinogenicity has been debated, considering the observation of these tumors particularly in rats (such as thyroid gland tumors), leading to the suggestion that endocrine disruption may be the cause of these tumors, but data supporting this hypothesis are limited (Bandarra et al. 2013). DNA adduct formation was also proposed as a mechanism responsible for the carcinogenicity of Acry (FAO/WHO 2002).

15 The Neurotoxic Effects

The neurotoxicity of Acry has been extensively studied since it was first reported in 1950. It is the most studied because it is the only toxic effect that has been demonstrated both in humans in protective occupational exposure and animal experiments; also, the nervous system is considered the preferred target of Acry (Erkekoglu and Baydar 2014; Semla et al. 2017; Matoso et al. 2019).

Based on experimental studies, Acry is neurotoxic for the central nervous system (CNS) and peripheral nervous system (PNS). It was initially recognized as an agent that induces peripheral neuropathies that are clinically manifested by motor disorders including alterations in locomotion and coordination and muscle weakness; these signs are observed both in animals and humans (Pennisi et al. 2013).

Indeed, early morphological studies suggest that the neurological abnormalities caused by Acry are due to distal axonal degeneration in the CNS and PNS caused by initial damage to nerve endings and subsequent retrograde degeneration of axons. However, recent studies show that Acry disrupts nerve transmission, resulting in changes in neurotransmitter release (LoPachin 2004; LoPachin et al. 1992; Kopanska et al. 2017).

The toxicity of Acrylic and its health costs are multiple. Thus, it is a concern of the entire population to take into account such effects regarding food security. Researchers and industries must henceforth make serious actions to mitigate such global toxicity.

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Correction to: Nutrigenomics and Transcriptomics for a Personalized Nutrition

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