Jennifer K. Chen
Jacob P. Thyssen
Editors

Metal Allergy

From Dermatitis to Implant and Device Failure

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Foreword

Contact allergy to metals has been recognized for centuries. The description of allergic contact dermatitis in bricklayers following skin contact with lime, along with the eczema rubrum caused by skin contact with mercury, provided the basis for the pioneering description of the skin disease 'eczema' by Thomas Bateman. It was also one of the first diseases where it was learned that a specific exposure can create a recognizable disease that may reoccur in the event of subsequent exposure.

With the Industrial Revolution, the isolation and use of metals exploded. Today, metals constitute the backbone in, for example, trains, cars, buildings, airplanes and many types of industrial machines. Thus, metals are indeed essential elements for modern society, both as a basic element but also in many sophisticated products.

Contact allergy to new elements has been typically first described among workers exposed to high concentrations or repeated handling of the metal in question. Epidemics of contact allergy have traditionally been seen in consumers at much later stages. The Dane Poul Bonnevie (1939) correctly described this sequence for nickel allergy, as industrial development resulted first in nickel dermatitis in workers and later in consumers. Dr. Bonnevie also introduced the first standard patch test series and described nickel, chromium and cobalt as common allergens among patients with eczema. Ever since, contact allergy to metals has been the most frequent cause of allergic contact dermatitis worldwide.

Importantly, metals may have many different adverse effects on human health, e.g. cancer, lung diseases and allergic contact dermatitis. The latter is undoubtedly the most frequent, affecting up to 20% of the general population, with nickel being the most prevalent. Regulations are now in force to protect workers and consumers against metal dermatitis. The more recent EU regulations for nickel and chromium exposure protect more than 500 million Europeans and serve as good examples of the public adverseness to allergic contact dermatitis from metals.

The editors of the present volume, Jennifer K. Chen and Jacob P. Thyssen, are personally active in many metal allergy research areas. Their network and collaboration with international leaders within this research area have paved the way for this excellently composed, organized and edited comprehensive textbook. It has been possible to assemble global research leaders from all topics. The book amalgamates knowledge about the use of metals, basic immunology, regulatory aspects, and both general and highly specific clinical

areas. It is the first compendium on metal allergy that encompasses all relevant metals. A similar text is not currently present. The book includes all the classic areas of metal allergy and also, for the first time, an in-depth overview on allergy to implanted metals. Uncommon and controversial manifestations have also been included for completeness.

This pioneering textbook on metal allergy is highly appreciated as it covers a need for combining old knowledge with new insights and possible new avenues of research. This text is useful for the clinician, covering relevant patient care recommendations. As it provides an in-depth understanding of exposure hazards for individual metals, both in the occupational and the consumer universe, this text is also meant to be useful for responsible industrial personnel and public health administrators.

December 2016

Torkil Menné
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Preface

It is unsurprising that metal allergy has become a subject we encounter almost on a daily basis, especially for any specialist in allergic contact dermatitis. After all, nickel has long been the most commonly positive allergen seen in patch testing, and metals are ubiquitous in our society. What was a surprise to us, however, was the lack of any reference text specifically dedicated to the nuances and details of detecting and managing metal allergy.

Aside from metals being common sources of contact sensitization that are often difficult to avoid, there are a number of challenging or controversial presentations of metal allergy that may be difficult to diagnose, from implant failure to systemic contact dermatitis after dietary exposure to metals. Thus, there is a clear need for a comprehensive resource that can be consulted for guidance in both common and rare scenarios. This text is meant to fulfill this unmet need and serve as an indispensable reference for all things metal allergy.

The editors are deeply grateful to each of our chapter authors, without whom this text would not be possible. We feel very fortunate to have learned so much from their expertise. We hope that you will benefit from this text as much as we have.

Redwood City, CA, USA — Jennifer K. Chen
Hellerup, Denmark — Jacob P. Thyssen
March 2018

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Part I

Metal: Overview

Use of Metals in Our Society

1

C. Peter Cutler

1.1 Introduction

"In truth, in all the works of agriculture, as in the other arts, implements are used which are made from metals, or which could not be made without the use of metals; for this reason, the metals are of the greatest necessity to man" [1].

Metals are essential to almost every aspect of our lives today—and they have been indispensable since the Bronze Age. We rely on metals for tools, food production, buildings, medical equipment, energy production, transport and communications. This chapter explores the properties and uses of metals which make them so valuable to society.

1.2 What Are Metals?

Metals are naturally occurring elements which are generally:

- Solid at room temperature (mercury is an exception)
- Opaque and lustrous
- Good conductors of heat and electricity
- Ductile (can be drawn into wire)
- Malleable (can be hammered into thin sheet)

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Melting points of pure metals range from mercury at −39 °C to tungsten at 3410 °C. Relative densities of pure metals (water is 1.0) range from lithium at 0.53 to osmium at 22.6.

Of the 90 naturally occurring elements on Earth, 66 are metals and another 7 have some of the characteristics of metals. However, from the Bronze Age until the seventeenth century, only a handful of those metallic elements were recognised and in common use: iron, copper, lead, gold, silver, tin and zinc. Most metals were still to be identified, purified and studied. Since then, there has been an explosion in identifying, understanding and using the unique characteristics of those 66 metals, with the result that aluminium, cadmium, chromium, cobalt, lithium, magnesium, nickel, platinum, silver, titanium, tungsten and others are now familiar names. The knowledge about these metals was key to the industrial revolution and the subsequent development of technologies which could hardly have been imagined 200 years ago—air travel and mobile phones, for instance. Up to 62 metals may be used in a smart phone, each with a unique function and with almost no possibility of substitution [2].

As civilisations have developed, so has our use of metals, which continue to be crucial for our economies and societies. The resulting socio-economic benefits of these changes have been huge: not just increased GDP, but improved production, storage and distribution of food; improved medical care; increased trade; easier and more efficient transport; and

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the whole field of computing, communications and access to knowledge. Of course, it cannot be claimed that metals alone were responsible for these developments, but they did play key enabling roles and continue to do so today, as discussed below.

1.3 Economic Impact of Metals

Table 1.1 lists the annual primary production tonnages for a selection of metals in 2014. This is a measure of the quantity of new metal being put into use each year. It shows that the use of iron mainly as steel is many times greater than the use of any other metals. The table also shows the approximate market value of that new production and illustrates both the scale and economic importance of the metals' industries. That is reinforced by the many applications for metals and alloys which are described in the rest of this chapter.

Table 1.1 The size and economic importance of the metal industries in 2014

Metal	Annual production, tonnes	Approximate value of production, US dollar millions
Aluminium	53,000,000	86,000
Beryllium	400	179
Chromium	11,690,000	23,100
Cobalt	91,400	2,350
Copper	22,600,000	104,000
Gold	3,020	128,000
Iron (as steel)	1,667,000,000	500,000
Lead	10,600,000	19,900
Mercury	2,900	49
Molybdenum	295,000	6,500
Nickel	1,947,000	19,000
Palladium	184	4,090
Platinum	146	5,050
Tin	374,000	7,070
Titanium (metal)	186,000	1,110
Zinc	13,600,000	31,100

British Geological Survey [3], LME [4], InfoMine [5], Chemicool [6]

1.4 Alloys

An important characteristic of metals is their ability to combine with each other to form "alloys". It is in the form of alloys that metals are mostly used, rather than as pure elements. The UN Global Harmonised System of Classification and Labelling of Chemicals (GHS) defines an alloy as:

> A metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot readily be separated by mechanical means.

Alloys are not simple mixtures and usually have properties which are not just a blend of the properties of the constituent elements. For example, steels—a well-known category of alloys—can have strengths many times that of their major constituent, pure iron. Even metals which look as if they are being used as pure elements may actually be alloys, for example, 18 carat yellow gold used for jewellery is an alloy containing 75% gold, the rest being silver, copper or other metals.

Alloys can be tailored to provide a combination of useful properties, for example, strong at very high temperatures, resistant to aggressive chemicals, magnetic or non-magnetic, not brittle at very low temperatures. As a result, metals are mostly used as alloys rather than as pure elements.

1.5 Corrosion

Corrosion is the gradual deterioration of a material as a result of chemical reaction with the environment, e.g. the familiar rusting of iron and steel. This can lead to change in appearance, reduced performance or even failure of components. It can also lead to interaction of the corrosion products with the human body if there is physical contact.

The corrosion rate of an alloy is not simply a linear function of the initial corrosion rate or of the corrosion rates of the constituent alloying elements. This is especially so when elements which can form a protective oxide layer are involved,

like titanium in titanium alloys or chromium in stainless steel.

The cost to the world's economies of corrosion is enormous. The global cost has been estimated to be $2.5 trillion per year [7]. Corrosion can be reduced or prevented by using a coating to keep the corrosive medium away from the metal, by electrochemical methods or by using an inherently more corrosion-resistant material such as a stainless steel. The choice should be made after considering the whole life costs of possible solutions.

1.6 Origin, Occurrence, Extraction and Refining of Metals

All metals were created in stars and supernovae. They were incorporated in the Earth at the time of its formation 4.5 billion years ago. Their relative abundance on Earth is the result of those creation and formation processes. Most metals occur in nature as minerals: chemical compounds of the metals, such as oxides, sulphides, silicates and carbonates. Exceptions are the relatively unreactive, "noble" metals such as gold and platinum, which are found in the metallic form.

"Ores" contain minerals in a sufficient concentration to make it economically worthwhile to extract and refine the constituents. Those economic concentrations may cover a wide range: a high-grade iron ore might contain >65% iron, whereas a high-grade gold ore might contain as little as 0.002% (20 parts per million) gold. It is common for ores to contain not just the primary metal of interest but other metals, which can also be extracted as valuable by-products. It can take several years and major investment to develop an ore body from discovery to commercial production. Ultimately it is the economics of supply and demand which determine the viability of mining a particular ore body and determine the market prices of metals.

As a result of geological processes, minerals and ores are not distributed uniformly in the Earth's crust. Ores may occur at or near the surface, where they can be recovered by opencast mining techniques, or they may have to be mined underground—a more expensive process. Once extracted, the ores are processed to remove the waste rock and to concentrate the minerals of interest. This is normally done near the mine to minimise the transport of large quantities of waste rock. Then the concentrates are processed thermally and/or chemically to extract and refine the metals. The final product is usually the pure element but it may be an alloy or a chemical compound, depending on the intended use. These refining processes are tailored to the ores, the metals being extracted and the eventual use, and it may be more economic to site them away from the mining operations. All the extraction and refining processes use considerable amounts of energy [8].

1.7 Selecting a Material for a Product

Just as there have been great advances in understanding and developing the properties of metals, so there have been great advances in non-metals—polymers in particular. Faced with this large number of materials, how does a designer select the right one for an application? Many factors must be considered, including:

- Mechanical properties
- Resistance to the operating environment, e.g. corrosion resistance, resistance to extreme temperatures
- Special physical properties, e.g. magnetism, thermal conductivity
- Interaction with other materials
- Ease of manufacture and forming
- Appearance
- Maintenance and expected service life
- Recyclability
- Availability
- Initial material cost and whole life cost
- Impacts on the environment, health effects and their risk management

Sometimes this analysis may lead to several practical options with similar performance.

However, for some demanding applications, there is often only one clear choice of material, which provides the required performance at an acceptable cost. There may be pressure to find a substitute for a material—perhaps to improve performance or for reasons of cost or environmental impact—but the same factors used to select the original material need to be considered in selecting an appropriate substitute. These factors are powerful drivers for development of new and improved materials—metal alloys included. At the same time, materials which have been used for many years are not necessarily made obsolete by new developments but remain important because of their unique combination of properties. For example, stainless steel kitchen sinks are still being chosen alongside resin sinks for aesthetic, performance and cost considerations.

1.8 Manufacturing with Metals

Alloys are usually made by melting the constituents—including recycled material—in a furnace, where adjustments can be made to achieve the desired composition, before casting into ingots or slabs for further processing into semi-finished products, e.g. blocks, plates, sheet, foil, bars, wire, ingots or powder. Many processes are then available to make the final product assembly, whether a cooking pan or a jet engine—including cutting, hot forming, cold forming, machining, joining, heat treatment and surface coating as necessary. Considerable development effort continues to be put into all these manufacturing processes to enhance their efficiency and to produce materials with improved properties, greater consistency, less waste and at lower cost.

1.9 Recycling

Metals are naturally occurring elements and are "used" rather than "consumed". At the end of a product's useful life, the metals can be recovered and reprocessed. They are 100% recyclable without loss of their properties. In many cases, where there is no need to separate the individual elements, the metals will be reprocessed as alloys. For example, stainless steel collected at the end of a product's life—whether from a spoon or a railcar—can be added directly to furnaces making new stainless steel. In this way, the overall energy used in the manufacture of stainless steel—its embodied energy—can be minimised, contributing to sustainability and reduced environmental footprint [8]. For this reason, scrap metals are valuable raw materials, something which has been recognised right from the first use of metals, thousands of years ago. Today there are well-established scrap recovery and processing routes for metals, which make a positive contribution to their sustainability. Nevertheless, improving the recovery efficiency remains important [9].

1.10 Metals, Health and Allergies

Some metals are regarded as essential in trace amounts for human health, including chromium, cobalt, copper, iron, manganese, molybdenum, selenium and zinc. At the same time, some metals and chemical compounds of metals can be harmful to human health above certain levels.

The term "heavy metal" is sometimes encountered, which is an attempt to link the toxicity or ecotoxicity of a metal with its density or atomic weight. Yet there is no such correlation and the term is effectively meaningless.

It is recognised that people can develop allergies to some metals and that nickel is one of the most common causes of allergic contact dermatitis. However, brief skin contact with a metal cannot cause an allergic reaction. The metal must be in solubilised form, which can happen from corrosion of the metal or alloy. There must also be a sufficient amount of the solubilised form of an allergenic metal from corrosion by body fluids or exposure to a sufficient amount of an allergenic soluble metal compound. In the case of alloys, an allergy may be caused by one of the alloying elements or an impurity, rather than the alloy's majority constituent.

The corrosion rate, the nature and concentration of the solution, the skin contact duration

and frequency, the amount of the solubilised allergenic metal ions, the threshold for an allergic reaction of these metal ions and the susceptibility of the exposed individual are all key factors in determining the extent of an allergic reaction. Understanding the clinical characteristics, incidence and mechanisms of metal allergies enables proportionate and effective risk management practices to be established which allow the continuing beneficial use of the metals concerned.

1.11 Applications of Metals Today

There is no space here to cover every metal and their applications. The metals described in this chapter have been selected to illustrate the major importance of metals to society today, the range of unique properties which metals show, the diversity of their uses and where skin contact is likely. This chapter includes metals which are recognised as allergens as well as those which typically do not cause allergies. Thus it provides a context for the detailed discussion of individual metals, their allergies and their risk management in the rest of the book.

Metals and their alloys remain indispensable and of major importance in many fields, from the manufacturing of products to key enabling technologies. Steel is by far the most widely used alloy, both by tonnage and by value, as illustrated in Table 1.1. Steel is all around us—in our homes, buildings, transport and factories. It is easy to see that the value to society is many times the intrinsic value of the steel. It is the same with other metals. Whilst some uses of metals have been superseded, in most cases innovation has led to new applications and sometimes new alloys and an overall growth in use of metals.

Security of supply of strategically important metals has long been a concern. Today the lists of critically important metals continue to grow [10]. One example is the "rare earth elements" (REEs) which are all metals. They are rare because their ores are widespread but low grade. They have become essential to the functioning of electronic devices as well as in the powerful magnets used in wind turbines. There are no effective substitutes.

Metals are also used in the form of chemical compounds. These may be raw materials for a further process, for example, the electroplating process in which a thin layer of a metal is deposited from a solution of a chemical compound of the metal: the compound is transformed in the process and none remains in the final metal product. In other uses, the compound itself may become part of the final article, such as pigments in ceramics or one of the active components in a battery—for example, nickel hydroxide in a nickel-metal hydride (NiMH) battery.

There is no doubt that in the past there were issues with the environmental and health impacts of metal mining, production and use—as there were for many other mining and manufacturing activities. Today, there is much more awareness of the need for ongoing actions to address these issues as part of a balanced approach to sustainability.

Whilst we cannot foresee the future for metals, we can expect that metal-based materials will continue to be developed and used in novel ways. New technologies such as nanoscale materials, smart materials and use of 3-D printing will open up even more opportunities.

1.11.1 Aluminium

Aluminium is the most widely occurring metal in the Earth's crust, 8% by weight. When first produced in the middle of the nineteenth century, it was more costly than gold, yet today it is one of the most widely used metals. It is characterised by its low density—only one third that of steel—good ductility and good thermal and electrical conductivity. It readily forms a protective oxide layer on the surface and so has good corrosion resistance.

Production of primary aluminium (i.e. from the ore) is an energy-intensive process. However, the durability of aluminium and the inherent recyclability of metals result in very much less energy being needed to recycle it than to produce

it from its ore [8]. Its recyclability has been well recognised for many years.

Among many other applications, aluminium can be rolled to a very thin foil, which is widely used in food packaging.

Copper, magnesium, manganese, silicon, tin and zinc among other metals are used as alloying elements to strengthen aluminium. Aluminium itself is also an important alloying element in superalloys (see Sects. 11.11 and 11.4), which operate at temperatures hundreds of degrees higher than the melting point of pure aluminium.

The combination of low density and high strength makes aluminium alloys a first choice for many transport applications where light weight is important, for example, aircraft. It is not as stiff as steel, but this can sometimes be compensated for in the design. There is increasing use in the automotive industry to reduce weight, and the transport sector now uses 27% of aluminium production.

A further 25% of aluminium production is used as alloys in the construction industry because of its strength, light weight and corrosion resistance.

Aluminium is also used for electricity transmission lines because of the combination of high electrical conductivity, low density and corrosion resistance. It is sometimes combined with a steel core for additional strength. The energy sector uses 13% of aluminium production, and there are further applications in IT equipment.

1.11.2 Beryllium

Beryllium is one of the lightest and stiffest metals. It had few industrial applications until the 1930s when it started to be used in aerospace. Today it is listed as a strategically critical metal. Beryllium is mostly used in copper-beryllium alloys which have good corrosion resistance, high strength and elastic modulus and good electrical conductivity. That makes them valuable for springs, electrical contacts and collectors. Their non-sparking nature makes them suitable for tools in mining and other industries where explosions are a hazard.

The combination of stiffness, light weight and dimensional stability lies behind the choice of beryllium alloys for the mirrors of advanced space telescopes.

Beryllium is almost transparent to X-rays and so is used for windows on radiography equipment.

1.11.3 Chromium

Chromium is the element which makes stainless steels "stainless". When chromium is cut and exposed to water or moist air, it rapidly forms an adherent, protective "passive layer" of oxide on the cut surface. If damaged, the passive layer reforms quickly, so providing continuing protection to the underlying metal. Steels containing more than approximately 10.5% of chromium show this "stainless" characteristic. Without the protection provided by the passive layer, the steel would progressively rust away—something we are all too familiar with in ordinary steels.

Stainless steel is not just one alloy. The addition of other alloying elements, including nickel, molybdenum, manganese, tungsten and nitrogen has enabled a wide range of stainless steels to be developed, each with their own combination of corrosion resistance, mechanical properties and physical properties to suit a wide range of applications—from interior and exterior panelling for buildings to withstanding the very corrosive conditions in chemical plants.

Stainless steels account for the use of about 90% of the annual chromium production.

Chromium is also one of the key alloying elements in some low-alloy steels where it improves the ability to harden the steel by heat treatment.

Chromium-containing chemicals are used in chromium electroplating as well as in the production of cement and leather tanning.

1.11.4 Cobalt

Cobalt is a shiny, grey, brittle metal which is very rarely used as a structural material in its pure form but almost always as an alloy or as a component of another alloy system.

Nickel and cobalt are next to each other in the periodic table and are frequently found together in nature, as well as in alloys and chemical compounds, where it may be unnecessary to separate them for the intended use. Nickel-based and cobalt-based superalloys also have a lot in common, including their strengthening mechanisms and applications in the hot parts of jet engines.

Cobalt-chromium alloys have good wear and corrosion resistance, making them suitable for engineering and prosthetic applications.

Like nickel, cobalt is ferromagnetic at room temperature. The two elements combine with aluminium to form the Alnico™ permanent magnets. Magnet performance improved with the development first of samarium-cobalt magnets and then with neodymium-iron-boron, which contains a small amount of cobalt. These are important in today's high-performance electric motors. There is also a range of soft magnetic materials based on iron-cobalt.

Cobalt additions can be made to the iron-nickel alloys to control the thermal expansion coefficient.

Cobalt is an excellent binder for tungsten carbide and other cemented carbides for cutting tools, and other applications where hardness and wear resistance are needed.

Historically, metallurgical applications were the most important for cobalt. However, cobalt-containing chemicals now account for almost 70% of end uses and are particularly important in modern rechargeable battery technologies. Other uses include as catalysts[1] in the oil and gas and plastics industries, in bio-pharmaceutical applications and in dyes. Familiar to artists, cobalt pigments (e.g. cobalt blue) have been used in paint, glass and ceramics for millennia.

1.11.5 Copper

Copper's unmatched combination of high electrical and thermal conductivity, mechanical properties, corrosion resistance, workability and ready availability makes it one of the most widely used—and widely recognised—metals. Some 60% is used in electrical cables, a further 25% in roofing and plumbing systems and 15% in engineering machinery.

Alloying copper with tin to increase the strength and hardness of copper was discovered in prehistoric times and was a sufficiently important technological advance, particularly for tools and weapons, that it is recognised in the eponymous Bronze Age. Bronzes with small amounts of other alloying elements are still used for bearings, seawater handling equipment and bells.

Brass, an alloy of copper and zinc, has also been used since ancient times. It is easily worked and machined, which has made it widely used for small engineering parts, taps and other water fittings, cartridge cases and decorative parts. Brass is used for trumpets and other musical instruments—the "brass" instruments—as a result of its malleability and acoustic properties. The properties can be improved by small alloying additions, such as lead to improve machinability.

Copper and copper alloy surfaces resist fouling by marine organisms. Fouling which does occur is relatively easily removed. The antifouling properties of copper were recognised hundreds of years ago. Copper cladding of wooden ships in the eighteenth century also protected the timbers from attack by marine organisms, hence the expression "to give a copper-bottomed guarantee".

Similarly, copper and copper alloy surfaces can be antimicrobial. This property can assist in controlling transfer of bacteria via touch surfaces.

Copper alloys readily with nickel to form the copper-nickel alloys. Their resistance to corrosion, good thermal conductivity and workability make them suitable for applications as diverse as marine heat exchangers and coins. Closely related are the nickel-silver alloys, which, in spite of their name, do not contain any silver! These copper alloys are whitened by adding nickel and zinc. They have been used for many years as the substrate for silver plating on cutlery and tableware—the familiar "EPNS", electroplated nickel-silver.

[1] A catalyst is a substance which increases the yield and speed of a chemical reaction but without being consumed itself.

1.11.6 Gold

Gold's unique combination of distinctive appearance, tarnish resistance, malleability and scarcity has made it a highly prized metal for thousands of years for jewellery, coins and bullion. The purity of gold is measured in carats, 24 carat being 100% pure gold. Twenty-four carat is too soft for some applications so it is alloyed with metals including silver, copper, palladium, zinc and sometimes nickel. Jewellery is commonly made from 9, 14 and 18 carat gold. Almost 80% of gold used each year goes into jewellery.

The number of new applications for gold has increased considerably in recent decades so that they now account for around 12% of gold use. Most notable is its use in electronics and computers. The high electrical conductivity and tarnish resistance make for consistent performance and excellent reliability of contacts and connectors.

Often gold is deposited as a thin layer onto a less expensive metal substrate. Nickel plating is frequently used as a substrate for gold plating because it gives a very smooth finish. Thin gold layers are being used as a lubricant in space equipment because of their low tendency to seize.

A thin layer of gold on the windows of buildings can reduce the infrared transmission both ways, so increasing energy efficiency.

Because of its biocompatibility, gold is used in dentistry and also plays an important part in medical diagnostics, implants and treatments.

1.11.7 Iron and Steel

Iron and particularly its alloy, steel (iron alloyed with carbon and other elements), are today the metal and alloys with the greatest usage both by tonnage and by value (see Table 1.1). About 50% of steel production is used by the construction industry, where there is no suitable substitute for the frameworks of high-rise buildings. The transport industry (road, rail, sea and air) uses 25% of steel production, machinery 14% and metal goods a further 14%.

The use of chromium, manganese, molybdenum, nickel and vanadium as alloying elements with carefully controlled heat treatments has enabled a wide range of high-performance steels to be developed which combine high strength-to-weight ratio with stiffness. These developments continue in, for example, the automotive industry where there is continuing pressure to reduce weight and increase performance. This has led to the development of a range of high-strength steels whose properties are tailored by careful control of composition and microstructure.

Many structural and engineering steels corrode (rust) in damp and aggressive environments. This corrosion can be controlled by the use of paint or other protective coatings on these materials, for example, zinc (see Sect. 11.16). Alternatively, stainless steels can be used which contain at least 10.5% of chromium with other additions, including nickel, molybdenum, manganese and nitrogen which enhance corrosion resistance, strength and magnetic properties. Their corrosion resistance and the resulting low levels of metal release make stainless steels very suitable for equipment where cleanability and hygiene are important, such as in food handling, pharmaceutical production, medical applications, water treatment, chemical plant and building cladding. As a result, the use of stainless steel has grown faster than the use of other alloys.

The appearance and durability of stainless steels are evident not just in iconic buildings such as the Chrysler Building (New York), Lloyds Building (London) and Jin Mao Tower (Shanghai) but also in many smaller structures, architectural details, building services, home appliances and other items in everyday use.

1.11.8 Lead

Lead has been used for thousands of years. The Romans used it extensively for water pipes—long before any health impacts were recognised. Pewter—a tin alloy sometimes containing lead—was used for tableware for many years.

Lead-tin alloys have a low melting point which makes them suitable for joining other metals by soldering. Recently, concerns about the health and environmental effects of lead have led

to restrictions on its use and to the development of lead-free solders (see Sect. 11.14).

The lead-acid battery came into and remains in widespread use for automotive starting. In spite of the battery's weight, it provides the necessary high current and cold weather performance. It continues to be used widely to provide standby power systems for hospitals, communication systems and other essential services. Batteries now account for 85% of the growing use of lead.

Lead chemicals were used in ceramic glazes, glass "crystal" and paint pigments. However, during the twentieth century, health and environmental concerns related to the use of lead and its chemicals resulted in a reduction in permitted uses and consequent reduction of emissions and exposure.

Other uses include radiation shielding, where its high density, high atomic weight and ready availability make it an economic choice.

Nearly 95% of lead is collected and recycled at end of life, making it one of the most recycled metals today.

1.11.9 Mercury

Mercury is the only metal which is liquid at normal room temperature, making it useful in thermometers and electrical switches. Amalgams (alloys of mercury) were used for dental fillings and for extraction of gold from its ore. Mercury compounds were used for antiseptic and antifungal treatments. However, many of those uses have been or are being phased out because of their impact on health and the environment. There is still some, but declining, use in thermometers and electrical switches.

1.11.10 Molybdenum

Molybdenum is an example of a metal which is not widely known but has a combination of properties which play a vital role in a wide range of applications—including medical—and emerging technologies. Many alloy steels achieve their high strengths as a result of comparatively small alloying additions of molybdenum—typically less than 1% having a major effect. These steels are used widely for engineering components throughout the transport, oil and gas, power generation and chemical industries. Consequently, 41% of the molybdenum produced is used in these steels.

Molybdenum is also added in small amounts to many stainless steels to improve their corrosion resistance, for example, in marine applications. This is another example of how a few percent of an alloying addition can have a very marked effect on properties. Modern alloy production methods allow the composition to be controlled within fine limits to ensure the effective and efficient use of the alloying additions. Stainless steel uses 22% of annual molybdenum production.

Molybdenum has a very high melting point but its density is significantly less than other "refractory" metals (e.g. tungsten). It is used for tools which operate at high temperatures and for handling molten metal and glass. It is an important component in superalloys (see Sect. 11.11).

The coefficient of thermal expansion of molybdenum metal is close to that of silicon, and it also has good electrical conductivity, making it a suitable substrate for silicon electronic devices. It also plays a key role in improving the performance of photovoltaic cells for solar electricity generation.

Of the molybdenum-containing chemical compounds, the best known is molybdenum disulphide which is used as a lubricant additive. The chemicals are used as pigments for paints and ceramics, corrosion inhibitors and versatile catalysts, accounting for 13% of molybdenum production.

1.11.11 Nickel

Nickel-containing alloys are indispensable and widely used today—a far cry from the days when German miners saw nickel as an unwelcome impurity in the copper ores they were seeking. Today nickel is a good illustration of the versatility of metals and their alloys.

About two thirds of the nickel produced is used in stainless steels (see also Sect. 11.7). Whilst it is chromium which makes stainless steels stainless, nickel improves strength, ductility, toughness (not brittle) and corrosion resistance. As a result, approximately two thirds of the stainless steel produced today is alloyed with nickel.

Corrosion resistance, formability, ease of cleaning and the ability to be sterilised have ensured that the stainless steels are used extensively in food processing, catering, water treatment, wine production, pharmaceutical plants and medical equipment. The use of stainless steels continues to grow faster than many other alloys.

Alloys based on 80% nickel with 20% chromium have been used for many years as heating elements—from domestic cookers to industrial furnaces. The addition of aluminium and titanium in particular, but also cobalt, molybdenum and tungsten, produces a further family of alloys often called "superalloys" because of their exceptional strength at temperatures over 1000 °C. They are stronger at these high temperatures than many materials are at room temperature. They are used in the hottest parts of the gas turbines (jet engines), which are widely used for power generation and aircraft propulsion. Without these alloys, modern, fuel-efficient air travel would not be possible.

At the other extreme of temperature, nickel-containing stainless steels remain tough (not brittle) to very low temperatures making them candidates for liquid natural gas (LNG) transport and storage, along with aluminium and iron-36% nickel alloy.

The iron-36% nickel alloy is remarkable in that it has nearly zero thermal expansion from low temperatures up to around 200 °C. For his discovery of this alloy, Guillaume was awarded the Nobel Prize for physics in 1920. Known as "Invar™", the alloy was originally used for pendulums for high-precision clocks. More recently, it was used extensively in colour television tubes—until display technology progressed. Today the alloy is used in the electronics industry as well as for linings in some designs of liquid natural gas (LNG) storage tanks. Other alloy compositions, including cobalt, have expansion coefficients tailored to match those of the plastics used for integrated circuit encapsulation—important for the external connections.

Nickel is one of only four elements which are ferromagnetic (strongly magnetic) at room temperature. The other three are the metals iron, cobalt and gadolinium. Alloys of iron and nickel are easily magnetised (soft magnets) and are particularly suitable for shielding sensitive electronic equipment from electromagnetic interference (EMI). Alloys of aluminium, nickel and cobalt give rise to the Alnico™ family of permanent magnets—the first mass-produced permanent magnets. Used for many years in motors and loudspeakers, these magnets are being superseded for many applications by stronger magnets using the rare earth elements (see Sect. 11.4).

Electrodeposition of nickel—electroplating—was one of the first commercial uses of nickel 150 years ago and produced an attractive, corrosion-resistant coating. It also provided a suitable substrate for other decorative coatings, especially chromium but also gold and other metals. Nickel-chromium plating has become very widely used for decorative and corrosion-resistant coatings. It is familiar in automobile trim, plumbing fittings and office furniture. Today electroplating accounts for about 10% of the annual use of nickel. Nickel plating reproduces the surface detail on the substrate very accurately. This is the basis of the electroforming process to produce screens for rotary screen printing of fabrics and the moulds for pressing CDs, DVDs and security holograms.

Nickel can also be deposited chemically. This "electroless" nickel plating can produce coatings for wear and corrosion resistance as well as providing a smooth substrate, for example, for the magnetic medium on discs of computer hard drives.

Nickel plays an important role in the structure and chemistry of several rechargeable battery technologies. Stand-by power, portable devices and electric/hybrid vehicles all depend on nickel.

Nickel has a long history of being used for coins. The Canadian five-cent piece or "nickel" was struck in pure nickel at times in its history, but since 2000 it has been struck in nickel-plated steel for cost reasons. An alloy of copper with 25% nickel has been and continues to be used widely for coins because of its silvery colour, corrosion resistance, ease of striking and durability.

Normally metals which have been deformed have no memory of their previous shape, but there are alloys which do have a memory and can reform to a previous shape when heated. An alloy of nickel and titanium in equal proportions is the best known of these "shape-memory alloys": formed at one temperature and then deformed at a lower temperature, it will return to its original shape when reheated. This property is exploited in medical devices and implants, for example, in stents which can be squashed and put into a blood vessel where they will re-expand at body temperature to open up the blood vessel. These alloys also exhibit "superelasticity", reversible elastic deformation many times greater than other metals, making them suitable for dental braces and spectacle frames.

Nickel-based catalysts are important in the production of hydrogenated vegetable fats, reforming hydrocarbons and the production of chemicals.

1.11.12 Palladium

Palladium is one of the platinum group metals (PGMs; see platinum). Like platinum, palladium is very resistant to corrosion at low and high temperatures and has strong catalytic properties. It is used in similar applications to platinum, vehicle catalytic converters being a major use.

Some palladium jewellery is made, but more frequently palladium is used as one constituent of white gold (see Sect. 11.6). It is also used in dentistry.

A unique property of palladium is its ability to absorb 900 times its own volume of hydrogen at room temperature and pressure. This property enables palladium to be utilised in purifying and storing hydrogen.

1.11.13 Platinum

Platinum is a dense, very unreactive (so very corrosion resistant), malleable, silvery, scarce and valuable metal. It is a potent catalyst. As a result, 45% of platinum goes into catalytic converters to control vehicle emissions and a further 10% is used in the chemical industry. The other major use for platinum is for jewellery because of its appearance, corrosion and wear resistance and value.

Platinum metal is biocompatible because of its corrosion resistance and low reactivity and so has many uses in medical applications. It has many niche applications in engineering which depend on its corrosion resistance, particularly at high temperature, for example, spinning molten glass. It is often used in conjunction with its neighbouring elements in the periodic table (ruthenium, rhodium, palladium, osmium and iridium), which are known collectively as the platinum group metals (PGMs).

A platinum 10% iridium alloy cylinder made in 1879 is the international prototype kilogram which remains to this day the world standard of mass. The alloy was chosen because of its high density, wear resistance and tarnish resistance.

1.11.14 Tin

Around 3000 B.C. the Bronze Age started with the discovery of the hardening effect of alloying copper with tin. Pewter—tin alloys containing small amounts of copper, antimony, bismuth, sometimes lead and silver—became widely used by the fifteenth century for domestic tableware. Tin alloys are still extensively used—as bronze, in wine capsules and, more recently, in lead-acid battery grids.

Lead-tin solders have been phased out of plumbing, electronic and other applications. They have largely been replaced by tin-based solders which can also be tailored to have precise melting ranges. Solder represents 47% of tin use today.

A thin tin plating on the interior of steel cans provides the corrosion resistance necessary for

the success of canning as a means of food preservation, which accounts for 15% of tin use. In some products, tin is in direct contact with food to provide anti-oxidant action, which preserves colour and taste.

Extensive use of glass is a feature of many buildings today. The glass must be flat, of uniform thickness and flawless. This has been possible by using the "float" process where the molten glass floats on a bath of molten tin during solidification. Tin is also coated onto glass for radiation insulation, conductivity and scratch protection.

Niobium alloyed with tin is the key constituent of the high field strength superconducting magnets used in medical scanners and in the Large Hadron Collider particle accelerator in CERN (the European Organisation for Nuclear Research in Geneva).

Tin compounds are used as catalysts, in ceramics and in plating baths, and to prevent the degradation of PVC building products by heat and sunlight. It is likely to continue being used in a wide variety of energy-saving materials.

1.11.15 Titanium

Titanium has the highest strength-to-density ratio of any of the pure metals. Its density is about half that of steel. It also forms a very adherent surface oxide film which makes it very corrosion resistant in many media, including seawater. It can be further strengthened by alloying, particularly with aluminium and vanadium. This combination makes it well suited to applications which require high strength with light weight, particularly in aerospace. It is used in compressor blades of jet engines and, more visibly, for the fan blades at the front of turbofan engines in which the fan generates most of the thrust.

About 44% of titanium metal production goes into aerospace applications, but it is perhaps not surprising that the same properties—particularly light weight—are exploited in some high-performance items of sports equipment, for example, in cycling, mountain climbing and golf.

Industrial uses of titanium are found in the energy, chemical, marine and desalination industries for heat exchangers, pipework and vessels. One high-profile architectural application is the titanium external cladding of the Guggenheim Museum in Bilbao, Spain.

Its biocompatibility, along with its other characteristics, makes titanium suitable for surgical implants and medical tools.

The above uses illustrate the versatility of titanium metal, but uses of the metal itself account for only 5% of the annual titanium production. The remaining 95% is used to produce titanium dioxide. This is a very white, stable powder which is unaffected by ultraviolet light and so is used as a pigment in paint, as a whitener in plastics, paper, food and toothpaste.

1.11.16 Zinc

The major use of zinc is for corrosion protection. When steel is in contact with zinc in a situation where the steel would rust, the zinc corrodes preferentially, protecting the steel from corrosion. The zinc can be applied as a coating on the steel—galvanising—either by an electrolytic process or by dipping the components into molten zinc. Galvanised steel handrails and fences are a familiar sight. Blocks of zinc ("anodes") can be fastened in contact with immersed structures and buried pipelines to provide cathodic protection.

Zinc has been used for many years in battery construction. Today zinc powder is used for alkaline dry cell batteries.

Brass, an alloy of copper and zinc, was being made in the first millennium BC from zinc ore and copper although it was not as easy to make as bronze because of the low melting point of zinc. With the production of elemental zinc metal in the fifteenth century AD, brass then became an important engineering material in the industrial revolution. It has an attractive combination of mechanical properties, corrosion resistance, ease of machining and fabrication, appearance and cost.

In addition to brass, zinc is also used as an alloying element in the nickel-silver alloys (see Sect. 11.11). Zinc alloys—often with aluminium—are used to produce small, intricate components by die casting, the injection of the molten alloy into a die under pressure where it sets quickly because of the relatively low melting point.

Around 25% of zinc is used as chemicals in diverse applications.

1.12 Summary

- Metals have been important to society since the Bronze Age and their use is still increasing.
- Metals are frequently critical to the success of new technologies.
- The specific and unique properties of some metals mean that they have very specific but important uses and cannot readily be substituted.
- Metals are used but not consumed and are therefore theoretically infinitely recyclable. However, improving the efficiency of recovering metals from products at end of life continues to be important.
- Exposure to an allergenic metal is not in itself sufficient to cause an allergic reaction. The metal must be in a solubilised form, and the exposure must be in sufficient amounts to provoke an allergic response.
- As the examples have shown, the opportunities for direct skin contact in most applications of metals, and hence the opportunities for an allergic reaction, are specific but limited.
- Understanding the science associated with metal allergies and where those metals are used is key to managing the risks of metal allergies and allowing safe use of metals and alloys in appropriate applications.
- Agricola's view of metals in 1556 still holds today, and metals remain indispensable for developing and maintaining a sustainable society. There are no signs of that changing in the foreseeable future.

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Metals and Corrosion

2

Morten Stendahl Jellesen

2.1 Introduction

Corrosion is a natural phenomenon for metals. In accordance with the laws of thermodynamics, metals after production and shaping return to their lower energy state: metal ore. Corrosion is the electrochemical dissolution of metals during which metals are released together with electrons (the oxidation process). At the same time, electrons are consumed (the reduction process). In total, the corrosion process is an irreversible reaction. Equation 2.1 shows the anodic reaction, i.e., metal oxidation, and Equation 2.2 the cathodic (reduction) reaction if the process takes place in an acidic environment (involving a reduction of H+). Equation 2.3 shows the reduction processes taking place if the corrosion process happens at neutral or alkaline electrolyte systems (involving a reduction of O_2, i.e., oxygen from the atmosphere or dissolved in the aqueous electrolyte).

$$M \rightarrow M^{n+} + n\,e^- \tag{2.1}$$

$$2H^+ + 2e^- \rightarrow H_2 \tag{2.2}$$

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^- \tag{2.3}$$

The anodic and cathodic reactions take place on the same metal surface, meaning that if the cathodic reaction is reduced, then also the anodic reaction is reduced in order to satisfy the conditions of having a zero net current. This means that corrosion can be limited by not only protecting the metal from anodic dissolution but also by reducing the reduction reaction (e.g., by limiting the amount of oxygen).

In a system with a metal and an electrolyte, several corrosion reactions can take place, with metal oxidation into metal ions (Equation 2.1) representing just one of them. This oxidation reaction leads to the formation of free ions that can diffuse into surrounding solution or become involved in the formation of metal oxides, metal chlorides, organometallic compounds, or other chemical species. In practice release of metals rarely happens as active dissolution resulting in free metal ions but as a more complex process involving passivation of the metal with metal release because of passive dissolution and transpassive dissolution or due to local corrosion phenomena happening on the metal surface. A general schematic of reactions taking place at a passive metal surface is given in Fig. 2.1.

For many metals and alloys, their stability is due to the formation of a thin oxide layer (the passive layer). Examples are aluminum (Al), titanium (Ti), and stainless steel (chromium (Cr)). The passive layer is spontaneously formed with

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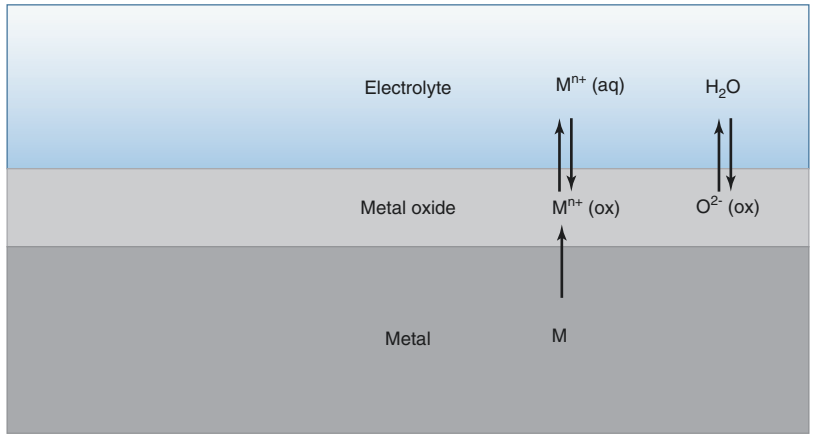

Fig. 2.1 Schematic of electrochemical reactions of a passive metal. Metal cations are generated in the interface of metal and oxide, and the ions migrate through the passive film and across the passive film/electrolyte interface. Anions of O^{2-} migrate from the electrolyte interface toward the metal. The overall result is the generation of a passive film on the metal surface

surrounding oxygen and protects against the environment. The protective properties of the passive film are due to the passive film acting as both an electronic barrier for electrons and also a physical barrier for cation and ion transport to the metal surface in the electrolyte. Known passivating metal alloys are stainless steel (chromium oxide), titanium, and aluminum alloys.

The degree of protection is determined by the rate of ion transfer through the film, as well as the stability of the protective film against dissolution. Chemical composition, structure, thickness, homogeneity, and the presence of defects are important parameters determining the level of protection that a passive film provides against metal dissolution. As for all corroding systems, the chemical composition of the electrolyte (especially pH and chloride content), the redox condition, exposure time, and temperature are also important parameters affecting the level of corrosion.

In some cases, transpassive dissolution can happen. This is when the protecting passive film is oxidized further into higher oxidation levels. Examples are biomaterials exposed to highly oxidizing media such as hypochlorite or hydrogen peroxide, in which the risk of forming Cr^{6+} in the transpassive region has attracted attention due to the high toxicity and carcinogenicity of Cr^{6+} [1].

Metals that do not form passive films are in their active or immune state. If electrochemical conditions are such that a metal is in its active state, this means that the metal forms a charge transfer reaction at the metal electrolyte with the result that the metal ions are released into the solution as ions (Equation 2.1). If the solubility of the metal ions in solution close to the surface is exceeded, a precipitation of corrosion products will occur on the metal surface.

Many corrosion attacks seen on passive materials are due to only localized corrosion attacks, where the remaining surface has an intact passive layer. The mechanism for localized corrosion is self-propagating, since a local site for anodic dissolution can alter the local electrolyte environment, and at the same time, there is a large area of the metal surface available for the corresponding cathodic reduction reactions. Pitting and crevice corrosion of stainless steel are well-known examples of local corrosion being accelerated at low pH in environments with a high amount of chlorides (Fig. 2.2).

2.2 Thermodynamic Considerations

The thermodynamic calculations for the stability of passive films on various metals can be illustrated in Pourbaix diagrams, known as potential-pH diagrams [2]. The schematic Pourbaix diagram given in Fig. 2.3 shows the regions of active dissolution, passivation, and immunity.

Fig. 2.2 The pictures to the *left* show crevice corrosion under a gasket in a stainless steel heat exchanger, and to the *right*, a stainless steel railing for a staircase leading into a swimming pool. In both cases, corrosion is initiated due to high chloride content and stagnant conditions in the crevice formed when assembling against polymer gaskets

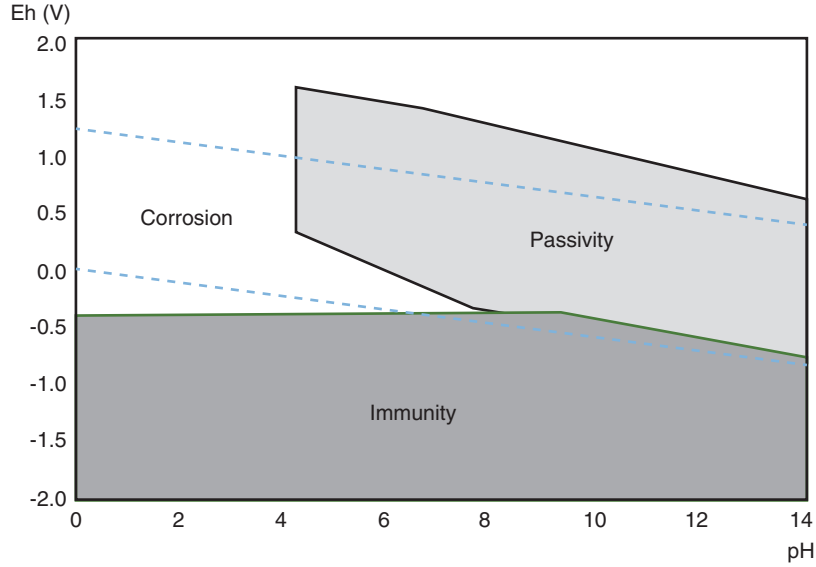

Fig. 2.3 Schematic Pourbaix diagram for stainless steel showing the regions of immunity, corrosion (active and transpassive dissolution), and passivation at varied pH and electrochemical potential regions. The *dotted blue lines* show the stability region of water

The tendency for individual metals to accept or donate electrons is given in the electrochemical series (Fig. 2.4). The higher E^0, the more noble the metal. Among the best known noble metals are gold (Au), silver (Ag), or platinum (Pt). The electrochemical series is given as calculated standard potentials at standard state conditions, meaning a concentration of 1 M at 25 °C. A change in electrolyte or temperature will change the potential values, e.g., gold is soluble in aqua regia (a mixture of nitric acid and hydrochloric acid), due to nitric acid being an oxidizer and chloride ions forming soluble complexing ions with gold.

Nickel and iron are examples of metals being less noble, with the least noble metals being zinc and magnesium. Due to the negative electrochemical potential of these metals, they can protect the less active metal to which they are coupled. This property is utilized when zinc and magnesium metals are used as sacrificial anodes for the protection of constructions or ships.

2.3 Electrochemical Studies of Corrosion Kinetics

In order to get a deeper understanding of a specific metal's corrosion properties, laboratory studies are commonly carried out. Electrochemical techniques, such as open circuit potential monitoring, potentiodynamic curves, and potentiostatic tests, can be carried out with a potentiostat as hardware and a three-electrode system. The three-electrode system consists of the metal as a working electrode, a reference electrode, and a

Electrode	E°/V
$Li^+ + e = Li$	– 3.045
$Ca^{2+} + 2e = Ca$	– 2.84
$Na^+ + e = Na$	– 2.714
$Mg^{2+} + 2e = Mg$	– 2.356
$Al^{3+} + 3e = Al$	– 1.67
$Ti^{2+} + 2e = Ti$	– 1.63
$Mn^{2+} + 2e = Mn$	– 1.18
$Cr^{2+} + 2e = Cr$	– 0.90
$Cr^{3+} + 3e = Cr$	– 0.74
$Zn^{2+} + 2e = Zn$	– 0.76
$Fe^{2+} + 2e = Fe$	– 0.44
$Cd^{2+} + 2e = Cd$	– 0.403
$Ni^{2+} + 2e = Ni$	– 0.257
$Mo^{3+} + 3e = Mo$	– 0.20
$Sn^{2+} + 2e = Sn$	– 0.136
$Pb^{2+} + 2e = Pb$	– 0.125
$Cu^+ + e = Cu$	0.520
$Hg_2^{2+} + 2e = 2Hg$	0.796
$Ag^+ + e = Ag$	0.799
$Pd^{2+} + 2e = Pd$	0.915
$Pt^{2+} + 2e = Pt$	1.188
$O_2 + 4H^+ + 4e = 2H_2O$	1.229
$Au^{3+} + 3e = Au$	1.52
$Au^+ + e = Au$	1.83

Fig. 2.4 Standard potentials of electrode reactions

counter electrode (Fig. 2.5). The purpose of the reference electrode is to measure the potential. The counter electrode is typically made of corrosion-resistant materials such as platinum or graphite, and its function is to act as the counterpart in the electrical circuit with the working electrode. With this configuration the potential of the working electrode can be measured against a reference electrode, and the potentiostat can monitor the current in the circuit while regulating the potential between the working and the reference electrode.

With a reference electrode and the metal of interest immersed in the same electrolyte, the open circuit potential can be monitored. The open circuit potential is the potential of a metal in a given electrolyte and in the absence of any applied external current, e.g., by a potentiostat. At the open circuit potential, the anodic and cathodic reactions occur simultaneously and at the same rate. Typically the open circuit potential is measured prior to further electrochemical studies in order to give the metal time to stabilize in the electrolyte. The open circuit potential measurement is useful since it provides information on the surface conditions of the metal in contact with the electrolyte, similar to the standard potential values given in Fig. 2.4, although in this case the potential value represents the actual metal (alloy) and a given electrolyte at a given temperature. The open circuit potential value as such represents the possible chemical reactions taking place at the surface, e.g., passivation reactions as sketched in Fig. 2.1, and the formation rate of a passive film can be monitored. The open circuit potential value increases until a steady-state value is reached as the metal is fully passivated.

A potentiodynamic measurement using all three electrodes gives the option of measuring the current density as a function of the applied potential, as the potential (viz., the reference electrode) is changing at a constant rate by the potentiostat. The result is a collection of both current density and potential data as shown in Fig. 2.6. Performing an open circuit potential measurement and creating a potentiodynamic curve are typically the first approach when studying a metal alloy in a given electrolyte. ASTM G5-94 [3] establishes a standard for measuring potentiodynamic curves where experimental conditions such as scan rate are suggested. It is important that the scan rate is sufficiently slow in order to permit steady-state mass transport conditions at the electrode surface.

As the anodic polarization scan starts, an increase of current density is seen. This part of the potential scan is where the metal is in its active state and is characterized by dissolution of the metal and formation of soluble ions that dissolve into the solution. The current density values monitored in this part of the potential scan can be

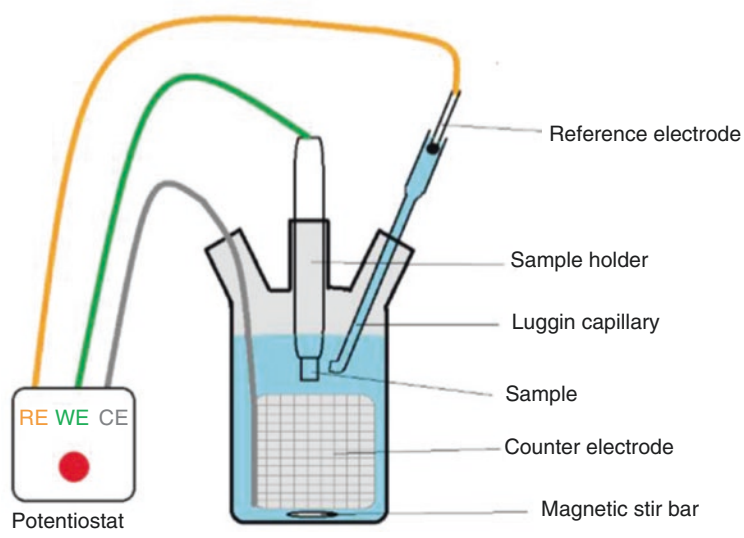

Fig. 2.5 Electrochemical measurement setup including potentiostat with connection to reference, working, and counter electrode. The setup allows for corrosion monitoring at various electrochemical potentials for different metal alloys, electrolytes, and temperatures

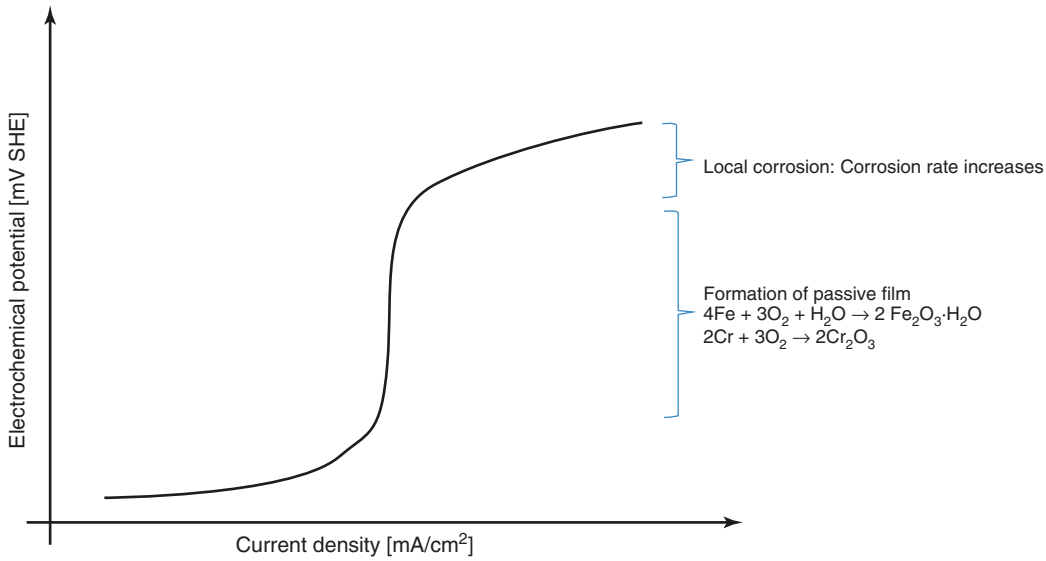

Fig. 2.6 Schematic representation of the anodic part of a polarization curve made on stainless steel in a nonaggressive electrolyte solution by the use of potentiodynamic measurement via a potentiostat and three-electrode setup. As the electrochemical potential is increased, the current density is monitored and represents passive layer formation (chromium and iron oxide for stainless steel) and shows the electrochemical potential where local corrosion is initiated

directly related to the corrosion rate of the metal in the electrolyte system via Faraday's law.

$$m = \frac{I \cdot M \cdot t}{n \cdot F} \tag{2.4}$$

In Faraday's law (Equation 2.4), m is the mass of metal dissolution over time, t and I are the anodic current, n the number of electrons, and F Faraday's constant (96,485 (C/mol).

As the potential is increased, the surface of the metal is covered by a passive film that decreases metal dissolution and thus current density. The passivation region is typically characterized by its passivation potential value (the

initiation of passivation) and the current density value of the passive region, representing the current density that runs through the metal and oxide as sketched in Fig. 2.1. The passivation current density thus represents the protective properties of the film: the lower the current density, the more protective the film is against dissolution.

At high electrochemical potentials, there can be local breakdown of the passive film (e.g., pitting corrosion of stainless steel in a chloride-containing electrolyte). This transpassive region of the polarization curve is characterized by increased current density; however, the total current can no longer be ascribed to metal dissolution or oxidation of the metal. If the electrochemical potential in the transpassive region is higher than the potential for water, some of the current running in the three-electrode setup will be a result of oxygen evolution due to water oxidation.

The placement of a given metal in the electrochemical series or the thermodynamic state illustrated in the Pourbaix diagram, together with experimental analysis using potentiostatic measurements, is the basis for describing a metal's interaction with any given electrolyte system. Whereas Pourbaix diagrams will supply thermodynamic information on the metal electrolyte interface, potentiostatic testing provides information on the kinetics of metal dissolution. More detailed studies can be performed with potentiostatic tests in order to evaluate the specific effects of factors such as temperature, chloride content or electrochemical potential on the structure, composition and thickness of formed passive layers, or active dissolution of metal.

2.4 Summary

Corrosion is the electrochemical dissolution and release of metals that occurs when a redox reaction takes place. Metal release can be directly related to the oxidation of a metal; however, many metals and alloys form a thin oxide layer that passivates the surface and decreases metal release. The degree of protection is determined by the rate of ion transfer through the passive film, as well as the stability of the protective film against dissolution. This lack of protection at high chloride containing environments explains the well-known examples of crevice or pitting corrosion seen for stainless steel in, e.g., a swimming pool environment. The state of a metal, whether it is in its active dissolution, passive, or immune state, can be thermodynamically illustrated by Pourbaix diagrams, showing the effects of electrochemical potential and pH. Corrosion kinetics and resulting metal release can be determined by electrochemical laboratory measurements.

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3 European Standards Developed in Support of the European Union Nickel Directive

Martin Baker

3.1 Nickel Directive

The incidence of nickel allergy was originally associated with occupational exposure among workers in the electroplating industry [1–3]. During the course of the twentieth century, there was, however, a significant increase in the use of nickel in consumer articles. Nickel allergy was observed via exposure to stocking suspenders, spectacle frames, jewellery, clothing articles and mobile phones [4–8]. The consequence of the application of nickel in such a wide range of consumer articles was to increase the significance of consumer exposure as opposed to occupational as the cause of sensitisation to nickel [9, 10]. By 1990, the prevalence of nickel allergy in Europe among females was approximately 10% and in males 1% [11].

On the 27th of June 1989, the Danish government introduced legislation [12] to prohibit the manufacture and import of nickel-containing consumer articles that exceeded a certain nickel release value. This regulation applied to nickel alloys and nickel-plated articles in the product categories of jewellery, watches and clothing. The aim of this regulation was to prevent primary nickel sensitisation occurring from consumer articles. A nickel release limiting value of 0.5 μg/cm^2/week was specified in this regulation. This release value was deemed to be a safe limit to prevent both sensitisation and elicitation of nickel allergy [11].

As a result of the increasing prevalence of nickel allergy in Europe and the introduction of national legislative initiatives [12, 13], the European Commission (EC) published a draft for a new European directive in 1993 [14] to limit the use of nickel. This directive consisted of three parts, each part introducing specific limiting values for nickel-containing consumer articles in applications involving piercing and prolonged and direct contact with the skin. Consumer articles that did not conform to the requirements of parts 1–3 of this directive would not be allowed to be placed on the market.

Part 1 of the directive regulated the use of post assemblies inserted into pierced parts of the body during epithelisation of the wound canal. For such post assemblies, two criteria were proposed for compliance with the directive: firstly that they were homogenous and secondly that the nickel concentration expressed as mass of nickel to total mass was less than 0.05%.

Part 2 involved nickel-containing consumer articles having prolonged and direct contact with the skin. Consumer articles coming into this category would only be deemed compliant if the rate of nickel release was not greater than 0.5 μg/cm^2/week.

Part 3 specified particular criteria to be applied to articles which were coated and stated in part 2, except where these articles had a nickel external

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coating. The rule for compliance for part 3 stated that, where a coating existed, this coating should be sufficient to ensure that the rate of nickel release from this article did not exceed 0.5 μg/cm^2/week for a period of 3 years of normal use. In addition to parts 1–3, the EC also stated in this draft directive that a mandate would be issued to the European Committee for Standardisation (CEN) to develop the European standards necessary to prove compliance with the regulations listed in parts 1–3.

This draft directive was voted upon by the European Parliament and then sent to the Economic and Social Committee. The EC, taking into consideration the various comments on the draft directive, published their common position in 1994 [15] and finally adopted on the 30th of June 1994 Directive 94/27/EC [16], more commonly known as the "Nickel Directive". In comparison with the original draft, directive parts 1–3 remained almost unchanged except that in part 3 the requirement of 3 years of normal use was reduced to 2 years. There were, however, significant changes to the regulations concerning the date of adoption of the directive by the European member states. The date of entry into force of the Nickel Directive was firstly made dependent upon the date of publication in the *Official Journal of the European Communities* (OJEC) of the CEN standards required to show conformity with the directive. Furthermore the European Parliament tabled proposals to introduce specific time periods ranging from 6 to 18 months, in order to give manufacturers, importers and retailers sufficient time to ensure that non-compliant articles no longer entered the marketplace.

Before the publication of the Nickel Directive, initial work had already been started on developing analytical methods by the CEN technical committee (TC) 283 "Application in jewellery and associated products". This development work started in 1991 following a Swedish proposal to extend the scope of CEN/TC 283 to include working group 4 (WG4) "Health and safety aspects with special reference to nickel allergy". Accordingly the EC issued a mandate M/004 which directed CEN/TC 283 (WG4) to develop the analytical methods required to prove conformity with the Nickel Directive.

The initial work of WG4 had concentrated on developing the analytical methods for parts 1 and 2 [17]. For part 1, the proposed analytical method involved acid dissolution of the test article, followed by measurement of the nickel concentration using atomic spectrometric analysis. For part 2, the proposed test method for nickel release determination involved placing the test sample for 1 week in a solution of artificial sweat, followed by measurement of the ensuring nickel release using an appropriate analytical method. The clinical relevance of this test method was verified by comparing patch testing results from nickel-sensitised individuals using a variety of consumer-relevant nickel-containing materials with the ensuing nickel release values [18]. For part 3 of the Nickel Directive, an accelerated wear and corrosion test based upon a modification of international standard 3160-3 [19] was proposed to simulate 2 years of normal use [20]. This method comprised of suspending the test article above a corrosive medium, followed by tumbling the article with abrasive chips and finally evaluating the nickel release according to part 2. Additionally WG4 had also started to develop a screening method based upon dimethylglyoxime to detect nickel release from consumer articles.

The completion of the experimental work necessary for the development of the mandated standards, including drafting the standards for the associated CEN voting procedures, was completed by WG4 in 1998. In the CEN formal voting procedure, the proposed standards received the necessary number of votes from the CEN members to achieve approval as European standards (EN). The EC published references to these EN in the OJEC in 1999 [21]. The final legal adoption of the Nickel Directive in Europe occurred in 2001 following the expiration of the associated transition periods. The additional standard developed by WG4 based upon dimethylglyoxime was published as a CEN report in 2002.

Since the introduction of the REACH regulation [22] in 2007, the restrictions concerning nickel in consumer articles have been included in entry 27 of Annex XVII of REACH.

3.2 EN 12472

EN 12472 (1998) "Method for the simulation of wear and corrosion for the detection of nickel release from coated items" is the test method responsible for checking conformity with part 3 of the Nickel Directive. This standard is a pragmatic approach to simulate accelerated wear and corrosion from a wide variety of coated articles coming into direct and prolonged contact with the skin. The metallurgical composition, shape, temperature and the characteristics of the wearer have a profound influence upon the degree of wear and corrosion of an article. The first stage attempts to simulate accelerated corrosion by sweat, by suspending the parts of the test article that come into direct and prolonged contact with the skin, over a mixture of lactic acid and sodium chloride for 2 h in a thermostatically controlled oven at 50 °C. After completion of the corrosion stage, the test article is subjected to accelerated wear by tumbling for 4 h in a plastic cylindrical container with a wear medium consisting of an aqueous solution of a surface active agent and cylindrical corundum chips. After completion of EN 12472, the quantitative nickel release of the test article is determined using the standard responsible for part 2, EN 1811.

Shortly after consumer articles started to be tested according to this standard, concerns began to arise about the application of the wear medium to spectacle frames. In order to resolve this issue, the EC requested CEN to prepare an alternative standard for accelerated wear and corrosion for spectacle frames. The CEN technical board passed a resolution in September 2000 requesting CEN/TC 170 "Ophthalmic optics" to prepare a European pre-standard (ENV) for the simulation of wear and corrosion for the detection of nickel release from spectacle frames. The proposed ENV 14027 was based upon the accelerated wear test referenced in ISO 12870 "Ophthalmic optics—Spectacle frames—General requirements and test methods". This ENV served as a temporary standard specifically for spectacle frames, therefore enabling them to be excluded from the scope of EN 12472. CEN/TC 283 WG4 in cooperation with CEN/TC 170 started a revision of EN 12472 to address the issue of spectacle frames. The focus of this revision was centred upon the wear medium and the tumbling equipment. As the present wear medium was considered inappropriate for the testing of spectacle frames, it was decided to replace this with a mixture of the outer shells of coconuts, walnuts, peanuts and almonds mixed together with an abrasive paste. The tumbling equipment was replaced by a barrel with a hexagonal cross section, which had the ability to reverse the direction of rotation. Additionally, the duration of the wear test was increased to 5 h, the direction of rotation being reversed after 2.5 h. Inside the barrel, the test articles were attached to a retaining assembly, instead of being placed directly in the wear medium. An annex A was introduced into the standard to give information about how to attach test articles to the retaining assembly. The revision of the standard was completed in 2005 and resulted in the withdrawal of ENV 14027, thus enabling again spectacle frames to be included in the scope EN12472. In 2007, the EC published the revised standard in the *Official Journal of the European Union* (OJEU) [23]. The last revision of EN 12472 occurred in 2008, resulting in a change to the method of preparation of the wear medium. The EC published a reference to this revision in the OJEU in 2012 [24].

3.3 EN 1810

EN 1810 (1998) "Body-piercing post assemblies—Reference test method for determination of nickel content by flame atomic absorption spectrometry" was the test method responsible for checking conformity with part 1 of the Nickel Directive. This standard specified how to determine the nickel content in a variety of metals and alloys commonly used in piercing post assemblies. The principle of the standard relied upon acid dissolution of the test article followed by determination of the nickel content in the resulting solution using atomic absorption spectrometry.

As part 1 of the Nickel Directive limited the nickel content in post assemblies to less than 0.05%, it excluded the use of certain types of

stainless steels. The EC responded by commissioning a risk assessment to investigate the risk of nickel sensitisation from post assemblies, in particular the issue of nickel release from stainless steels suitable for post assembly applications [25]. This risk assessment report concluded that it would be more appropriate to have a nickel release limit instead of a nickel content limit for post assembly articles. The scientific committee on toxicity, ecotoxicity and the environment (CSTEE) was requested by the EC to review this report [26]. In 2004, the EC amended part 1 of the Nickel Directive [27], replacing the nickel content requirement for post assemblies with a nickel release regulation. Therefore, for post assemblies to be placed on the market, the new regulation stated that the rate of nickel release must be less than 0.2 μg/cm^2/week. The European member states were instructed to adopt this regulation by September 2005.

3.4 EN 1811

EN 1811 (1998) "Reference test method for release of nickel from products intended to come into direct and prolonged contact with the skin" is the test method responsible for checking conformity with part 2 of the Nickel Directive. This standard forms the cornerstone of the nickel restriction regulations as it provides a quantitative measure of the nickel release. In principle EN 1811 attempts to simulate the biological reactions that occur when a metallic article comes into direct and prolonged contact with the skin.

The testing procedure of EN1811 can be seen as involving three basic stages: determination of which parts of the test article are to be tested and their surface areas, followed by the nickel release procedure and finally the measurement and assessment of the resulting nickel release value. Only parts of the test article that have prolonged and direct contact with the skin are to be tested for nickel release. Article parts that are not part of the test area must be either removed or coated with a wax or lacquer, which is capable of preventing the release of nickel. Due to considerations of analytical sensitivity, a minimum test surface area of 0.2 cm^2 should be tested, or if necessary two identical articles can be tested together to obtain this minimum area. Further information about identification, determination of test area and the application of waxes or lacquers was included in annex C of the standard. After the test area part and surface area have been determined and the application of a wax or lacquer has been completed, the test article can proceed to the nickel release stage.

The test solution for the nickel release procedure consisted of sodium chloride, urea and lactic acid dissolved in a litre of aerated water. By the addition of a diluted ammonia solution, the pH of this solution is adjusted to be in the range of pH 6.40–6.60. The test article is then suspended in a suitable container and a volume of test solution added corresponding to 1 ml/cm^2 test area. The test vessel is now closed and placed for a period of 1 week without agitation at a temperature of 30 ± 2 °C in a thermostatically controlled oven. After 1 week, the test article is removed from the test solution, rinsed with deionised water and stabilised with dilute nitric acid. The measurement of the nickel release is undertaken using an appropriate analytical spectrometer. In order to obtain the necessary analytical sensitivity, the spectrometer must be able to detect nickel at a limit of least 0.01 mg/l in the test solution matrix. To avoid matrix interference, the spectrometer is calibrated with standards having the same matrix as the test solution. The final test result is calculated as a release rate expressed in μg per cm^2 per week.

As this standard is based upon a release method instead of a content determination, it is inherent that significant statistical differences in the test results can arise. During the development of EN 1811, WG4 decided to follow the approach taken in the European standard for the migration of metals from toys [28]. In EN 1811, the analytical result is therefore multiplied by a factor in order to take into consideration parameters that are most likely to affect the statistical uncertainty of the nickel release test results. The factor incorporated into EN 1811 was 0.1; therefore in practice all nickel release test results were reduced by a factor of 10.

In addition to the nickel release test procedure, four annexes were included in this standard. Annex A provided information about the interpretation of results and the statistical reasoning behind the use of an analytical factor. Annex B provided detailed instructions concerning the manufacturing and application of a nickel release reference material. Annex C gave advice to laboratories on how to identify and determine the article test area and the application of a wax or lacquer to areas not considered to be part of the test area. Annex D was included in order to make manufacturers aware of particular metallurgical situations where the nickel release from an article made of a composite material might exceed the 0.5 μg/cm^2/week limit, although the individual components were compatible with this limit.

In 2004, the EC amended the regulation concerning post assemblies [27], which resulted in post assemblies being included in the scope of EN 1811; they were however excluded from the scope of EN 12472. Additionally this amendment included a request for CEN to undertake a revision of EN 1811 with special reference to the 0.1 factor. In 2007, the EC issued mandate M/414 requesting CEN to revise EN 1811. The responsibility for this revision was allocated to CEN/TC 347 "Methods for analysis of allergens" Task Group 1 (TG 1).

During the course of the revision, CEN/TC 347 passed a resolution to withdraw EN 1810 in order to acknowledge the nickel release regulation for post assemblies. The nickel release limit for post assemblies was therefore incorporated into EN 1811, which resulted in an amendment being published in 2008. The final draft of the EN 1811 revision was presented by TG 1 in 2010 to CEN/TC 347, including a request for a 2-year date of withdrawal period of the current version. The revised version of EN 1811 passed the CEN formal voting procedure in 2011 and was referenced in the OJEU in 2012 [24].

In comparison to EN 1811 (1998), the major differences concerned piercing articles, the preparation of the test solution, the interpretation of the nickel release results and the annexes.

In order to accommodate piercing articles, the title of the standard was changed to include a reference to piercing articles. The composition and method of preparation of the artificial sweat test solution was investigated by TG 1 by testing various alloys and modifications of the artificial sweat solution. As a result, TG 1 decided to replace the ammonia solution used to adjust the pH value of the test solution with a solution of sodium hydroxide. Furthermore, unaerated water was used instead of aerated water in the test solution preparation.

For the issue of the analytical factor, it was decided to follow the approach of measurement uncertainty as outlined by Eurochem [29]. The interpretation of the nickel release results was therefore amended by replacing the one-sided analytical factor with a statistically justified measurement uncertainty limit measurement, which would be used for compliance assessment of the test article. Annex A was completely rewritten to explain to laboratories the relationship between the analytical result, the expanded measurement of uncertainty and the compliance assessment procedure.

In annex B, only the composition and physical parameters of the reference material were now included. For annex C, it was decided to provide detailed information on how to prepare test articles prior to nickel release testing. A procedure was outlined for assessing which parts of the test article come into direct and prolonged contact with the skin or are inserted into pierced parts of the body and how to proceed with complex articles. Specific guidelines were also included on how to prepare watches and a variety of jewellery articles, including piercing articles. In annex D, further advice was included for manufacturers about unsuitable material compositions for nickel release, in particular with relation to the use of nickel either as an interlayer or in cases where it is coated with a protective coating.

During the revision of EN 1811, a proposal was made to develop a nickel release standard specific for spectacle frames and sunglasses. In 2010, EC mandate M/448 was assigned by CEN to CEN/TC 170 "Ophthalmic optics", with the request to develop this standard. The responsibility for the development of this was assigned to CEN/TC 170 WG 8 "Nickel release testing of

spectacle frames". Accordingly, spectacle frames and sunglasses were excluded from the scope of the revision of EN 1811. As now no standard was available for spectacle frames and sunglasses, it was agreed as an interim solution to republish the original version of EN 1811 with a new EN number 16128 but limiting the scope only to spectacle frames and sunglasses [24].

The method developed by WG 8 involves two distinct phases, a modified nickel release test procedure as compared to EN 1811 and a new development for the testing of nickel release from the organic coated surfaces of spectacle frames. For nickel release testing, the method involves placing test papers impregnated with artificial sweat on those parts of the spectacle frame most likely to come into direct and prolonged contact with skin. The spectacle frame is then placed in a thermostatically controlled oven at 30 ± 2 °C with a nominal humidity of 90% for 1 week. The nickel released into the test papers is then extracted followed by quantitative determination using an appropriate analytical method. As the majority of spectacle frames have an organic coating covering a nickel-containing substrate, WG 8 examined the possibility of developing a test method to measure the nickel release from these surfaces. An appropriate method was found by applying electrochemical impedance spectroscopy (EIS) to detect nickel, thereby giving an indication of the coating quality with respect to the release of nickel. In 2015, EN 16128 passed the CEN formal final voting procedure.

With the publication of the revision of EN 1811, concerns arose about the interpretation of the compliance assessment criteria for the nickel release testing results. In 2014, CEN/TC 347 WG 1 proposed an amendment to clarify the compliance assessment procedure. Accordingly, the parts of the standard concerned with compliance assessment were amended in order to give a clear statement about when the nickel release value of an article would be deemed to be non-compliant. In terms of compliance assessment, articles having a nickel release limit of 0.5 μg/cm^2/week would be deemed to be non-compliant when the nickel release value is greater than or equal to 0.88 μg/cm^2/week. For articles having a nickel release limit of 0.2 μg/cm^2/week, an article would be deemed to be non-compliant when the nickel release value is greater than or equal to 0.35 μg/cm^2/week. The amendment to EN 1811 was referenced in the OJEU in 2016 [30].

3.5 CR 12471

CR 12471 "Screening tests for nickel release from alloys and coatings in items that come into direct and prolonged contact with the skin" is a qualitative test based upon the reaction of nickel with dimethylglyoxime in the presence of ammonia. The results obtained in using this screening test do not constitute confirmation of compliance of the test article with respect to the Nickel Directive. This test method does, however, offer a quick, simple and inexpensive procedure to indicate the release of nickel from consumer articles. This method is suitable for manufacturers and importers to detect the presence of nickel in imported articles or as a quality control procedure to give a qualitative indication of the nickel release arising in the manufacturing stages of nickel-containing articles.

The test procedure involves rubbing the surface of the test article with a cotton swab moistened with ammonia and dimethylglyoxime. For the testing of coated items, it is recommended to abrade the surface of the test article, particularly in cases where a negative result has been obtained on an unabraded article. Additionally, the sensitivity of the test can be increased by treating the test area prior to the application of the cotton swab with artificial sweat and heat.

The appearance of a red colour from light pink to strong cerise indicates that the nickel release of the test article is probably exceeding the 0.5 μg/cm^2/week limit. In cases where the nickel release approaches the 0.5 μg/cm^2/week limit, the sensitivity of the test method to detect nickel at these levels becomes an important consideration. It is therefore recommended to use EN 1811 or, when necessary, EN 12472 followed by EN 1811, in cases where the colouration obtained is very weak, negative, or the colouration due to nickel is masked by the presence of interfering metals.

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Chromate Testing in Leather: EN ISO 17075

4

Ines Anderie and Kerstin Schulte

4.1 Chromium in Leather Articles: Allergenic Potential

Allergic reactions to leather products are quite common in the population. Skin rash and allergic symptoms, caused by wearing leather articles, can be observed in sensitized people. There is a broad range of articles made from leather for everyday use such as shoes, jackets, gloves, belts, purses, dog leashes, chairs, sofas, or auto interiors, and the risk of sensitization is omnipresent. One of the major allergens described for leather is chromium(VI) [1, 2]. The potent leather allergen chromium(VI) represents one of the oxidation states of the elemental chromium. In general, most of the chemical elements exist in different oxidation states, varying in energy level and chemical reactivity.

The most important oxidation states of chromium are chromium(0), chromium(III), and chromium(VI):

- Chromium(0) is the metallic form and a component of several metallic alloys.
- Chromium(III) is a component of chromium salts, which are used for leather tanning. Chromium(III) does not induce skin irritation, as its permeation through human skin is very low. Under certain conditions, even chromium(III) can cause allergic reactions (see Chap. 27). In the aqueous environment, chromium(III) is present at acidic pH values below pH 7.0.
- Chromium(VI) is very reactive and often used for chemical-induced oxidation processes. Chromium(VI) salts are toxic and highly caustic, and direct skin contact leads to skin damage and poorly healing ulcers. Chromium(VI) is a potent allergen, and sensitization due to repeated skin contact is possible. In the aqueous environment, chromium(VI) is present at alkaline pH values above pH 7.0.

Chrome tanning is the most commonly used method to preserve leather. Around 80% of the leathers produced worldwide are chrome tanned. The tanning process requires a lot of expertise, as the procedure is very complex and different chemicals need to be used. In a preliminary step, the hide is cleaned of meat leftovers, hair, and fat. The tanning process is carried out then by using chromium(III) salts or by using a combination of chromium(III) salts and further tanning agents, like vegetable or synthetic tannins. Chrome-tanned leathers contain huge amounts (10,000–80,000 mg/kg) of chromium(III), which is needed for the tanning process. During the leather tanning process, chromium(III) intercalates with the collagen fibers of the wet skin. This creates a stable skeletal structure and allows drying of the

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skin without shrinking. The resulting chrome-tanned leathers are durable and are characterized by a high strength and extremely good ductility and malleability. Thanks to its special properties, chrome-tanned leather can be found in diverse uses for almost all kinds of leather goods, among others footwear, clothing, furniture, or car leather. According to current knowledge, the use of chromium(III) salts for leather tanning is safe. If leathers are produced according to the best available technologies using modern high-end chemicals, there is nearly no risk for the generation of chromium(VI) in leather or leather articles [3, 4].

Under certain conditions, chromium(III) in leather can be oxidized to the potent allergen chromium(VI) [5, 6]. However, the use of obsolete technologies and chemicals in leather production and leatherworking, poor storage and transport conditions, heat, low relative humidity, light, and mold can lead to the formation of the potent allergen chromium(VI) out of the chromium(III) tanning salts in leather and leather articles [2, 7, 8]. Therefore, if chromium(VI) is detected in a leather article, its source is in most cases not clear. As shown in Fig. 4.1, this chemical process is reversible, and already-generated toxic chromium(VI) can be converted back to chromium(III) by using reducing agents, minimizing the generation of chromium(VI) during tanning, and creating a so-called reductive potential in the leather. This protects the leather against oxidation, leading to drastically decreased formation of chromium(VI) during the manufacturing process, storage, and transport. This treatment is not only suitable for the raw material leather, but it is also possible to post-treat already-finished leather or leather articles with reducing agents either to prevent chromium(VI) generation or to remove chromium(VI) [5]. Leather

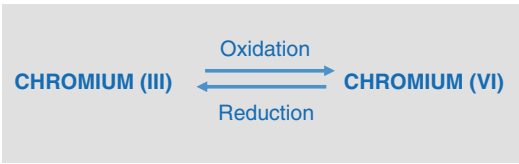

Fig. 4.1 Schematic representation of the conversion process of chromium(III) into chromium(VI)

items should not form chromium(VI) beyond the period of marketability. Wearing leather goods may also trigger leather aging processes, which could lead to oxidation to chromium(VI). Wearing of leather items should be possible without risk to health for a reasonable period of time. A preventive treatment of leather or leather products with a reducing agent is recommended.

4.2 Legal Regulation of Chromium(VI) in Leather Articles

Due to its potent allergenic potential, German health authorities enforced a national limit for chromium(VI) in 2010 [9]. The same limit was proposed by Denmark for the EU as well. The limit entered into force within the EU with regulation [10] as amendment of Annex XVII of the REACH Regulation [11]. Since May 2015, it is forbidden to bring leather products to the market that contain chromium(VI) above 3.0 mg/kg. Despite this legal regulation, there are nearly each week recalls of chromium(VI) containing articles published in RAPEX, a European Internet platform created for customer protection to warn consumers about dangerous products. The high number of non-compliant articles shows that the issue of chromium(VI) analyses in leather is still highly relevant [12].

4.3 Treatment of Leathers or Leather Articles with Reducing Agents for the Elimination of Chromium(VI)

Chromium(VI)-containing products are not marketable. The main cause of chromium(VI) generation in chrome-tanned leathers over time is the transformation of chromium(III) into chromium(VI) due to oxidation. This process is reversible, as chromium(VI) and chromium(III) are interconvertible by oxidation-reduction processes (Fig. 4.1). This reversibility is utilized in posttreatments of leathers and leather articles with

reducing agents. Usually spray applications of reducing agents (e.g., ascorbic acid) are applied to the chromium(VI)-containing leather items. This posttreatment eliminates chromium(VI) from the raw material leather and also from already-produced leather articles like a shoe or a jacket [8]. Professional re-conditioners are able to provide this service for complete product batches, which allows the trader to bring the revised leather articles back to the market. This posttreatment may not be successful in some cases. Depending on the worked-up leather and further materials on a given article, a rework might not work or lead to stains on the product. Whether chromium(VI) elimination by posttreatment leads to long-term success needs to be discussed carefully for each contaminated leather product.

4.4 Methods for the Measurement of Chromium in Leather

Several chemical methods and different parameters are available to receive more detailed information on the chromium content of leather. Some of the methods take into account the intended use and try to simulate the wear situation. Some of the extraction solutions used for determination have a sweat-like salt composition, and some extraction methods are carried out at temperatures between room temperature (20 °C) and body temperature (37 °C). On the other hand, some methods simulate exposure to heat and light during production, storage, and transport of leather articles and may give hints as to whether chromium(VI) generation due to oxidation of chromium(III) may occur in the life cycle of a leather.

4.4.1 Determination of Chromium(VI) Content According to EN ISO 17075

This method is used to determine whether the legal limit for the potent allergen chromium(VI) of 3.0 mg/kg is adhered to. Direct determination of chromium(VI) content in the leather matrix is currently not possible. Therefore, according to the standard EN ISO 17075, an extraction of the leather has to be executed prior to the determination of chromium(VI) in leather. The leather is either milled or cut into small pieces, then placed into an extraction vessel, and shaken within a buffer solution for 3 h. Afterwards, the leather parts are filtered off, and the content of chromium(VI) within the extract is determined. Determination of extracted chromium(VI) can be carried out by two different methods, photometry and ion exchange chromatography.

4.4.1.1 Photometry

For photometric measurement, the colorless reagent 1,5-diphenylcarbazide is added to the extract. In the presence of chromium(VI), the reagent is oxidized to a pink-colored chromium complex, which allows the quantitative photometrical determination of chromium(VI). A critical point of this method is the parallel extraction of dyestuffs from the leather that results in heavily colored extracts. The dyestuff may interfere with the photometrical determination of the pink-colored chromium complex. In that case, interfering substances need to be removed by solid-phase extraction (SPE) before adding the 1,5-diphenylcarbazide reagent.

4.4.1.2 Ion Exchange Chromatography

The determination of chromium(VI) content with ion exchange chromatography is state of the art, and modern technical equipment is needed. The technique allows determination of chromium(VI) content directly from the extraction solution. Chromium(VI) is separated on an ion exchanger column and the amount determined, after formation of the above-described pink-colored chromium complex or without derivatization directly at the corresponding UV-wavelength of chromium(VI) absorption. Due to the separation on the ion exchanger column, usually no interference of dyes occurs, and therefore no purification with solid-phase extraction is needed.

The amount of chromium(VI) found in the extract measured by photometry or by ion exchange chromatography refers to the amount

of chromium(VI) in the leather, and the content can be calculated. The detection limit of this method is 3.0 mg of chromium(VI) per kg of leather. The conditions for extraction must be followed exactly as described in EN ISO 17075; otherwise, there is a risk of false-positive or false-negative findings. The extraction should always be carried out in a single test, and extraction of mixed samples with more than one leather for chromium(VI) determination is not recommended. Incorrect false-negative results may occur if one of the leathers in a mixed sample has a reductive potential, which may prevent the identification of a possible chromium(VI)-loaded leather by reduction to chromium(III).

4.4.2 Spot Test

Recently, Danish scientists [13] described a spot test for the determination of chromium(VI) in leather and metal alloys, which should allow the detection of chromium(VI) directly on a leather article, without sample preparation. They used the reagent 1,5-diphenylcarbazide for direct application on a leather and determined chromium(VI) presence by observing a color change on the leather to pink. Based on our experience, handling the reagent 1,5-diphenylcarbazide is complicated, and colored leathers may lead to false interpretation of color change. Furthermore, the leather is damaged at the spot where the reagent was applied. In order to avoid false-positive or false-negative results, the determination of chromium(VI) according to EN ISO 17075 under controlled conditions in a test lab is advised [14, 15].

4.4.3 Determination of Recovery Rate According to EN ISO 17075: Influence of Leather Matrix

During the tanning process, the leathers are treated with several reagents to obtain the required characteristics. Some of them may have a reductive potential, which may influence chromium(VI) determination. In addition, even finished leather or leather articles may be treated with reducing agents, either to prevent chromium(VI) generation or to destroy chromium(VI) in contaminated leathers. Influences of the leather matrix can be detected by measuring the recovery of a known concentration of chromium(VI), which has been added to the extraction solution from EN ISO 17075. After the addition of a known amount of chromium(VI), the sample is worked up identically to the methods described in Sect. 4.4.1, using photometry or ion exchange chromatography. In normal cases, the recovery rate should be above 80%. In leather samples that were treated with reducing agents, the recovery rate may even drop to 0%, indicating that the reductive potential of the leather was strong enough to reduce the added chromium(VI) directly to chromium(III).

4.4.4 Determination of Chromium(VI) Content: Aging

Chromium(VI) may be generated in leather under certain stress conditions like heat and light. Heat and light influence the leather matrix. Due to these heat and/or light aging processes, the skeletal leather structure may disrupt, leading to an increase of unbound chromium(III) and its oxidation to chromium(VI) (Fig. 4.3). Another effect of heat and light aging may be degradation or inactivation of reducing agents, which were added to the leather to prevent oxidation. These processes may increase chromium(VI) formation and lead to concentrations above 3 mg/kg [16]. In their life cycle, leather and leather articles are often exposed to higher temperatures or light, e.g., via outdoor storage in the sun, the heat setting during production, transport in an overheated container, or storage in hot warehouses or behind showcases. To simulate these aging processes under lab conditions, the leathers can be aged artificially by heat and UV light:

- Heat aging: Leathers are heat-aged for 24 h at 80 °C in an incubator with a relative humidity below 5%. Thereafter, the above-described

determination of chromium(VI) according to EN ISO 17075 is performed.
- UV-light aging: Leathers are aged for 24 h with xenon light in a lighting unit. Thereafter, the above-described determination of chromium(VI) according to EN ISO 17075 is performed.

Some leathers react strongly to heat aging or UV aging with increasing amounts of chromium(VI). On the other hand, a lot of leathers survive these stringent heat or UV aging processes without showing any chromium(VI). Therefore, lab tests on the raw material evaluating for chromium(VI) by applying these aging conditions can serve as a support in deciding which leather can be used for the production of leather articles.

4.4.5 Determination of Soluble Total Chromium(III) Content According to EN ISO 17072-1

Chromium(III), which is used for tanning, is usually strongly bound to collagen fibers. Washing processes after tanning remove loosely attached chromium(III) from leather, so that only small amounts of chromium(III) should be released by wearing leather articles or using leather products. Nevertheless, some persons may react to a higher soluble total chromium(III) content with skin reactions (see Chap. 27) [17]. Therefore, this parameter is usually tested only on leathers that will have direct skin contact, e.g., lining leathers. In contrast to EN ISO 17075, where chromium(VI) is analyzed, soluble total chromium content can be determined using method EN ISO 17072-1. The test method imitates wear situations. The leather is cut into small pieces and incubated at 37 °C in a sweat-like, slightly acidic solution. During incubation, the leathers are not destroyed. The release of chromium(III) is determined either by atomic absorption spectroscopy (AAS) or inductively coupled plasma (ICP).

4.4.6 Determination of Chromium(III) Content After Total Digestion According to EN ISO 17072-02 to Classify a Leather as "Chrome Tanned" or "Chrome-Free Tanned"

The complete content of chromium in leather can be determined after complete disruption of the leather by total digestion. Measurement of total content of chromium is tested according to EN ISO 17072-2 or 5398 part 1–4. The leathers need to be digested completely by using strong acidic solutions and microwave treatment. Determination of chromium in the digestion solution will be usually performed using either AAS or ICP.

4.4.6.1 "Chrome-Tanned," "Chrome-Free-Tanned," or "Chrome-Free" Leather

The content of chromium is a benchmark to classify a leather as "chrome tanned" or "chrome-free tanned." The total content of chromium in a leather depends on the tanning process, on the washing and fixation, on the leather itself, and on the properties it should have. In chromium-tanned leathers varying concentrations of chromium can be found, grading from 10,000 to 80,000 mg/kg. For leathers with total chromium below 1000 mg/kg, it can be assumed that the leather is tanned without the intentional use of chromium(III) salts (per EN 15987), and these leathers can be classified as "chrome-free tanned." Small amounts of chromium may result from contaminated equipment, water, and chemicals, e.g., chromium-based dyes [18–20]. However, these leathers should not be described as "chrome-free leather." For "chrome-free leather," the total content of chromium should be as low as possible, as is technologically feasible. Chromium is a naturally occurring trace element, which is found in animals. Therefore, each leather will have small amounts of total chromium per se. For chromium-free leathers, some requirements advise that the content of total chromium should not exceed 20–50 mg/kg.

Synthetic or vegetable alternative tanning agents are available for chrome-free-tanned leather. Currently only a few tanneries use this technology because it is difficult to produce smooth and tear-resistant synthetic or vegetable tanned leathers. However, one can observe a growing demand for these chrome-free alternatives to avoid any health risk. Nevertheless, recent studies from Thyssen et al. [21] observed in some individuals an allergic reaction caused by chrome-free-tanned leathers, indicating that the use of chrome-free alternatives must be considered carefully.

4.5 Correlations Between the Different Test Parameters for Chromium in Leather

In a research project funded by the "Deutsche Forschungsgemeinschaft," we tried to identify correlations between the different parameters for chromium in leather [8]. We expected to find some simple rules which could easily be followed by the tanneries, thereby minimizing the risk of generation of the toxic chromium(VI) in leather. Three leathers with varying total chromium contents according to EN ISO 17072-02 were manufactured. No increase of chromium(VI) could be observed with increasing the total chromium used for tanning. Nevertheless, a correlation between the content of total soluble chromium and total chromium was found, as total soluble chromium increased with higher levels of total chromium (Fig. 4.2).

As already mentioned above, heat aging and UV aging may lead to increasing chromium(VI). Both aging processes were developed to simulate conditions to which the leather can be exposed during its life cycle, such as manufacturing, transport, or storing processes. We investigated the aging effects on upper leathers and lining leathers of shoes and found an obvious difference between upper leather and lining leathers (Fig. 4.3). Upper leathers are thicker and much more stable than lining leathers, which are often very thin and very soft, indicating that the tanning process is different. Chromium(VI) generation has increasingly taken place in lining leather, under normal conditions as well as under heat or UV aging.

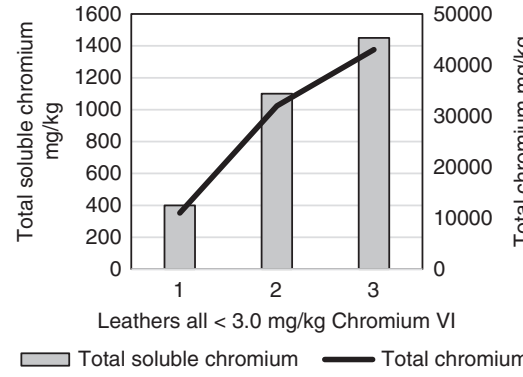

Fig. 4.2 Correlation between chromium(VI) EN ISO 17075, total chromium EN ISO 17072-02, and total soluble chromium EN ISO 17072-1 [8]

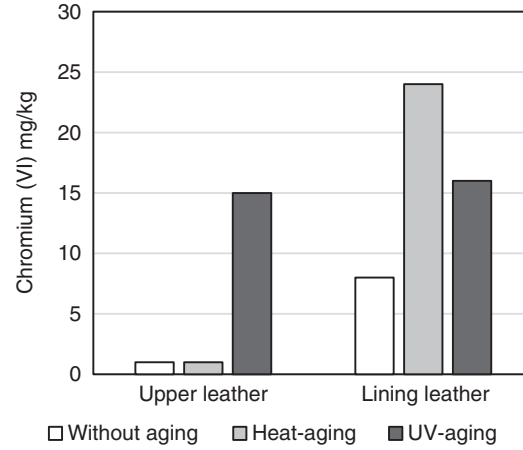

Fig. 4.3 Chromium(VI) generation in upper leather and lining leather for shoes under the influence of heat aging or UV aging [8]

Not only aging processes during the leather life cycle may lead to chromium(VI) generation in leather. Other processes during tanning are also critical, e.g., pH value, which should not be too alkaline. The pH value of the tanning baths should be controlled carefully. In addition, some posttreatments which are necessary after the tanning process are considered to induce chromium(VI) generation, like bleaching of the leather with oxidizing reagents or refatting the leather with unsaturated fat liquors.

Table 4.1 Correlation between chromium(VI), total soluble chromium (EN ISO 17072-1), and total chromium EN ISO 17072-2 [8]

Leather tanned using	Chromium(VI) EN ISO 17075	Total soluble chromium EN ISO 17072-1	Total chromium EN ISO 17072-2
	mg/kg		
Modern fat liquor	<3.0	749	37,947
Non-saturated fat liquor	8.1	787	36,005

Table 4.1 shows a comparison of leathers which were refatted by treatment with either a so-called modern fat liquor or the unsaturated fat-liquor fish oil. One could see that the amount of total chromium and total soluble chromium are nearly identical for both leathers, whereas chromium(VI) dramatically was induced by treating the leather with the unsaturated fat-liquor fish oil. Unsaturated fat liquors are easily oxidized, leading to free radicals, which may support chromium(VI) generation. Therefore, modern fat liquors should be used for chrome tanning, as they usually prevent chromium(VI) generation and protect the leather.

4.6 Prevention of Chromium(VI) in Leather and Leather Articles

The generation of chromium(VI) in chrome-tanned leathers can be avoided if some rules are followed. The leathers should be tanned with the best and latest know-how, and modern high-end chemicals should be used. Storage, transport, and processing steps at higher temperatures are unfavorable, and mold formation should be avoided during the whole life cycle of the leather or leather article [16, 22]. In recent years, the tendency has been increasingly to prepare leathers without chromium(III) salts. These so-called chromium-free-tanned leathers are either tanned with vegetable tanning agents from tree barks or fruits (e.g., oak, quebracho, chestnut) or with synthetic tanning agents. The number of different synthetic tanning agents is large, ranging from the traditionally used formaldehyde resin condensates and glutaraldehyde, to modern, lab-designed synthetic compounds. Nevertheless, even if there is a wide selection of chromium(III) alternatives, the use of some of them may be considered partially unfavorable with respect to effects on human health and the environment. However, one should also note that small amounts of up to 1000 mg/kg chromium(III) can still be present in chromium-free-tanned leathers (see above). For those sensitive to chromium, it should be ensured that the leather product is free of chromium. So far there is no protected designation with an exact specification as to how much chromium is acceptable in a so-called chrome-free leather. Leather is a natural product, and small traces of chromium will always be present.

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5 Metal Exposure Regulations and Their Effect on Allergy Prevention

Kate Heim and David Basketter

5.1 Introduction

Some causes of contact allergy have proven to be both common and persistent. Of these, there are contact allergies where regulation of the health problem is largely not possible, for example, poison ivy dermatitis in North America or parthenium dermatitis in India. Allergies from other causes, however, are susceptible to improvements through risk assessment and/or risk management. For example, fragrance allergy has been the subject of both of these strategies, with improvements to risk assessment being demanded, as well as risk management measures involving better communication of allergen content, and even the prohibition of certain allergens (e.g. [1, 2]). In this chapter, two common and persistent causes of allergic contact dermatitis, nickel and chromium, will be considered, specifically in relation to the impact that the imposition of specific regulations (i.e. risk management measures) has had on the burden of skin disease. Of course, it is important to note that the regulations applied to these metals are very different in nature, two being rather general restrictions applying to metal objects in prolonged contact with skin (nickel) [3] and leather products (chromium) [4] and the third applying to a quite specific problematic product used in the construction industry (chromium in cement) [5]. Nevertheless, there are both positive outcomes on which to reflect, as well as lessons to be learned concerning the value of communication and the need to fill important data gaps which continue to hinder more effective management of the risks to human health.

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5.2 Nickel

5.2.1 Background

Nickel is considered to be a weak sensitiser [6–8], with the amount of exposure needed to cause nickel allergy or nickel allergic contact dermatitis (Ni ACD) being relatively high compared to other dermal allergens. The historical and current prevalence of nickel allergy has been due to frequency and type of nickel exposure, not to the high strength (or potency) of nickel as an allergen. Nickel allergy was first noticed in occupational scenarios where nickel salts were being produced or used [9]. As a form of nickel that is readily solubilised in water or sweat, nickel salts were the primary source of nickel allergy and Ni ACD in occupations where there was significant skin exposure to these salts. Awareness of the source of the problem resulted in workplace changes to decrease skin exposure and associated

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nickel-allergic reactions. Occupational causes of nickel allergy and Ni ACD from exposure to nickel salts are uncommon these days.

Paradoxically, increases in non-occupational sources of nickel allergy followed the decline in occupational causes, though the non-occupational sources were due entirely to materials containing nickel metal (i.e. alloys, nickel-plated items, etc.). Ni ACD was initially observed in individuals who had prolonged skin contact with clothing items releasing nickel, such as nickel-coated suspenders, buckles, zippers, and clasps [9]. The incidence of Ni ACD increased with the growing use of nickel-plated jewellery. The most common cause of nickel allergy and subsequent Ni ACD is body piercing. Inserting nickel-releasing studs into the piercing wound to prevent closure during healing provides an even more direct route of nickel exposure than contact with intact skin. In addition, the conditions within a piercing wound are conducive to corrosion which facilitates release of solubilised nickel ions into the surrounding area. Once healed, with the piercing stud removed, Ni ACD may occur through additional contact with high nickel-releasing jewellery items in the pierced holes.

Ni ACD has also been more recently (since 2000) associated with individual cases of direct and prolonged contact with portable computers, mobile phones, and other handheld electronic devices (e.g. [10, 11]). Surfaces of these devices were coated with nickel, which was used to provide an appealing surface finish or for electromagnetic shielding. Recognition of these items as sources of Ni ACD is leading to modification of many of these products to the use of materials that do not release significant amounts of nickel for those parts that come in direct contact with the skin.

5.2.2 The Regulations

The first regulatory action taken to reduce nickel allergy and Ni ACD came into force in Denmark in July 1989 under Statutory Order no. 472 (Ministry of the Environment (Denmark)) [12]. Items produced before the enforcement date were allowed to be sold until January 1991, thus making this the date when all of the nickel-releasing items on the market in Denmark would have to be in compliance. This regulation restricted nickel release for specific consumer items to no more than 0.5 μg Ni/cm^2/week if the surface coating contained nickel [13]. Items included (1) ear ornaments or ear stickers; (2) necklaces, bracelets and chains, anklets, finger rings, and nail clips; (3) back of wristwatch cases, watch straps, and tighteners; (4) spectacle frames; and (5) garments equipped with buttons, tighteners, rivets, zippers, and metal marks which will by normal use come into close and prolonged contact with the skin. Compliance was determined by the dimethylglyoxime (DMG) test, which uses a cotton swab with liquid chemicals that react with available nickel ions. If a sufficient amount of available nickel is present, then a pink to red colour is evident on the swab to indicate failure of the DMG test. Failure of the DMG test by the items listed above meant they were not allowed for sale by manufacturers or importers in Denmark. The basis for this release rate was a study investigating a number of nickel-containing materials which were tested for nickel release comparing the release rate to patch test reactivity of those materials in nickel-allergic individuals [14]. Nickel release testing was measured using a basic synthetic sweat test as well as the DMG test. The nickel release rate limit of the materials that cause significant Ni ACD in patch testing was similar to the detection limit for the DMG test [14, 15]. The DMG test is much easier and less expensive to use than the synthetic sweat test, which explains the decision to use the DMG test as the measure of compliance. The Danish regulation was expected to reduce the number of cases of Ni ACD but would not necessarily protect every individual from Ni ACD [13]. "This regulation will not prevent all cases of nickel sensitization in the future, as some people might still develop nickel allergy from objects negative to the dimethylglyoxime test and releasing less than 0.5 μg nickel/cm^2/week".

Sweden enacted legislation in 1990 restricting ear piercing with nickel-containing piercers or rings made of alloys containing more than 0.05% nickel or having a nickel coating of more than

0.1 μm thick [16]. These values were based on the detection limits for nickel by atomic absorption at that time. The focus on piercing materials was due to the strong association of nickel allergy and ear piercing [17–22].

In 1992, the German Ministry of Health declared labelling mandatory ("Contains nickel"), if a product remaining in prolonged contact with the skin (e.g. jewellery, tools, and textile accessories) released more than 0.5 μg/cm^2/week [23].

Due to the difficulties posed by differing and/or lack of regulation among European countries, a European initiative combining the existing Danish and Swedish nickel regulations was adopted in 1994 as the Council Directive 94/27/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1994:188:0001:0002:EN:PDF). This was the 12th amendment of Directive 76/769/EEC on restriction of the marketing and use of certain dangerous substances and preparations. To briefly summarise, the European regulation (known as the EU Nickel Directive) specified that:

1. Post assemblies inserted into pierced skin were limited to less than 0.05% nickel;
2. Nickel release was limited to less than 0.5 μg Ni/cm^2/week for parts of products intended to come into direct and prolonged contact with the skin, such as those items specified in the Danish nickel regulation.
3. Products intended for direct and prolonged contact with the skin that have a non-nickel coating should meet the nickel release limit of 0.5 μg Ni/cm^2/week for at least 2 years of normal use.

The nickel content limit was based on the Swedish regulation. The nickel release limit of 0.5 μg Ni/cm^2/week was adopted based on the research that supported the Danish regulation, primarily the information from Menné et al. [14]. The intent of the EU and Danish regulation was to protect most of the population, but not necessarily every single individual. Standardised test methodologies were developed for compliance testing, but not until 1998, thus delaying the implementation of the EU Nickel Directive. The EN 1810:1998 standard [24] was used for body piercing assemblies as the reference test method for determination of nickel content by flame absorption spectrometry. The reference test method for the release of nickel from products intended to come into direct and prolonged contact with the skin was EN 1811:1998 [25], a standardised synthetic sweat test. Although the DMG test was researched for use as a reference test method (CR 12471 [26]), it was decided that it was not sufficiently accurate for compliance since it did not detect all high nickel-releasing items that caused positive patch tests in nickel-allergic individuals [15]. For simulation of wear and corrosion of coated items, EN 12472:1998 was developed (European Committee for Standardization (CEN), 1998c) [27]. This method was updated in 2005 and again in 2009 to make it more realistic for normal handling and use over a 2-year period [28, 29].

In 2004, the directive was amended (Directive 2004/96/EC [30]) to modify the requirement for post assemblies, so that this restriction would also be based on nickel release rather than nickel content. This release rate was lower, being 0.2 μg Ni/cm^2/week, compared to items intended for use in direct and prolonged contact with skin surface (0.5 μg Ni/cm^2/week) to address the fact that the epidermal layer was compromised during piercing exposure, providing less of a barrier for nickel to cross the skin barrier. This change from a regulation on nickel content to nickel release for piercing items was based on targeted RA study performed on LGC report "Risks of sensitisation of Humans to Nickel by piercing post-assemblies" [31]. There was recognition that piercing materials made of high-grade stainless steels used in surgical implants (ISO 5823) would not meet the content limit of 0.05% nickel but would release a very low amount (if any) of nickel [14, 32–34] and had low patch test reactivity [14, 35]. The release rate of 0.2 μg Ni/cm^2/week was ratified by the European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) in their opinion of November 2003 (http://ec.europa.eu/health/ph_risk/committees/sct/documents/out211_en.pdf). Recital 3 of the amended directive also

recognised an "adjustment factor" of 0.1 to be applied to the release rate result measured according to EN 1811:1998 to compensate for inter-laboratory variation and difficulty with measuring surface area of items. The European Committee for Standardization (CEN) was invited to review this standard so as to reduce this adjustment factor appropriately.

The original EN1811:1998 methodology and corresponding adjustment factor of 0.1 were updated in 2011 [36]. This version of the standard (EN1811:2011) introduced an uncertainty interval in place of the previous adjustment factor for:

- Post assemblies: non-compliant = 0.35 μg Ni/cm^2/week, compliant = 0.11 μg Ni/cm^2/week, and no clear decision = >0.11 and <0.35 μg Ni/cm^2/week
- Items intended for direct and prolonged contact: non-compliant = 0.88 μg Ni/cm^2/week, compliant = 0.28 μg Ni/cm^2/week, and no clear decision = >0.28 and <0.88 μg Ni/cm^2/week

Due to a number of concerns with the EN1811:2011 methodology, including failure of materials that were generally considered to not cause Ni ACD and the uncertainty resulting from the "no decision" category, EN1811 was amended in 2015 [37]. This updated version, which is the current one, resulted in an uncertainty adjustment of the acceptable release rate: <0.35 μg/cm^2/week for post assemblies and <0.88 μg/cm^2/week for items intended for direct and prolonged skin contact. Also in 2011, a separate reference test method was provided for spectacle frames [38]. This method was to specifically evaluate the release of nickel from parts of spectacle frames and sunglasses intended to come into close and prolonged contact with the skin.

With the implementation of the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), many of the previous individual directives, including the EU Nickel Directive, were subsumed under REACH. The nickel restriction was included as entry 27 in Annex XVII, which came into force in June 2009 [39]. The only change compared to the previous independent directive was the use of the term "articles" instead of "products" for consistency with the REACH terminology.

Two official clarifications have been made to the EU nickel regulation. One is that coinage is not covered under the EU nickel regulation [40, 41]. This is at least in part due to the targeted risk assessment done by the Danish authorities in the context of the EU Existing Substances Risk Assessment of Nickel [41–43] which concluded that there was a lack of evidence of any effect of coinage in causing Ni ACD in consumers and that additional studies were not considered necessary. The second clarification is that mobile phones are covered by the restriction and should comply with the release limit, as their use involves "direct and prolonged contact with the skin" [41, 44]. This is now included in the question and answers section on restrictions on the ECHA website [44].

Of outstanding concern was the definition of "prolonged contact" in order to determine what articles should be considered covered by the scope of the restriction. In 2011 the European Chemicals Agency (ECHA) was asked to assess the issue, and a definition paper was presented to Competent Authorities for REACH and CLP (CARACAL) in late 2013. This paper was endorsed by CARACAL in April 2014 and was included as a Q&A to clarify the existing regulation [45]. The agreed definition was:

> "Prolonged contact with the skin is defined as contact with the skin to articles containing nickel of potentially more than
>
> - 10 minutes on three or more occasions within two weeks, or
> - 30 minutes on one or more occasions within two weeks.

The skin contact time of 10 minutes applies when there are three or more occasions of skin contacts within a two-week time period. The skin contact time of 30 minutes applies when there is at least one occasion within a two-week time period".

In addition to the definition of "prolonged contact", the CARACAL members requested further guidance and clarification in the form of a list of articles to be considered falling into the scope of this new definition. ECHA was formally asked to derive this list of articles, with input from various stakeholders. The ECHA draft list of articles is expected to be available for public consultation in late 2016 or early 2017.

In North America, ASTM International has developed standards for children's jewellery [46] and adult jewellery [47] which also mimic the EU nickel restriction, including reference to the standardised test methodology. However, ASTM standards are not required, so no regulation currently exists in North America.

ASTM F2923 – 14 for children's jewellery states:

Section 10.1—*"Migration of nickel in any post assemblies of children's jewelry which are inserted into pierced ears and other pierced parts of the human body shall not exceed 0.2 µg/cm²/week (migration limit)"*.

Section 10.2—*"Migration of nickel in metal components of jewelry intended to come into direct and prolonged contact with the skin shall not exceed 0.5 µg/cm²/week. Items covered include:*

(1) components of earrings (other than post assemblies),

(2) necklaces, bracelets, chains, anklets, finger rings,

(3) wrist-watch cases, watch straps and tighteners".

Section 10.3—*"Where the components used in items listed in 10.2 have a non-nickel coating such coating shall be sufficient to ensure that the rate of nickel release from those parts of such articles coming into direct and prolonged contact with the skin will not exceed 0.5 µg/cm²/week for a period of at least two years of normal use of the article"*.

Section 10.4—*"Precious metals listed in Table 2, and stainless or surgical steel grades 304, 316 and 430, are expected to comply with the requirements of 10.1 through 10.3 and do not require further testing for nickel migration"*.

Section 10.5—*"Reference: EN 1811: 2011; CR 12741: 2002; EN 12472: 2009"*.

Table 5.1 Approved materials for adult body-piercing jewelry. With kind permission from ASTM [47]

Surgical implant stainless steel
Surgical implant grade titanium
Niobium (Nb)
Solid 14 karat or higher white or nickel-free gold
Solid platinum
A dense, low-porosity plastic, including, but not limited to, Tygon or Polytetrafluoroethylene (PTFE) if the plastic contains no intentionally added lead

ASTM F2999 – 14 for adult jewellery states:

Section 6.1—*"Body-piercing jewelry shall be made exclusively of the materials listed in Table 5.1"*.

Section 10.1—*"Representations regarding the safety of adult jewelry for adults sensitive to nickel or the limited potential for nickel to be released from metal components of adult jewelry shall be based on reasonable and representative tests, analyses or compositional assessments suitable for the application. Reasonable and appropriate test methods include, but are not limited to, those identified in 14.6. Precious metals listed in Table 2, and stainless or surgical steel grades 304, 316 or 430, are expected to meet these requirements and do not require testing"*.

Section 10.2—*"Reference—EN 1811: 2011; CR 12741: 2002; EN 12472: 2009"*.

5.2.3 Evidence of Effectiveness

Numerous studies have investigated the changes in the prevalence of nickel allergy using patch test data (using nickel sulphate hexahydrate) to evaluate the effectiveness of the early regulations in Denmark, Sweden, and Germany in the early 1990s, followed by the later EU Nickel Directive (Table 5.2) [48–58]. However, as others have done (personal communication), the authors of this chapter also would suggest that the regulation itself is a major, but not sole, part of the reason for the observed decrease in nickel allergy. Education and communication about nickel allergy and Ni ACD associated with the implementation of the regulation likely also played a

Table 5.2 Overview of changes in the prevalence of nickel allergy in young people of various European countries before and after nickel regulation

Country	Year	# of patients tested			Positive to nickel (%)			Reference
		Male	Female	Total	Male	Female	Total	
Denmark (clinical population)	1985–1986 (Age 0–18)			145			24.8[a]	Johansen et al. [50]
	1997–1998 (Age 0–18)			120			9.2[a]	
Denmark (general population)	1990 (Age 15–22)	28	48		0	16.7		Nielsen et al. [52]
	1998 (Age 15–22)	76	102		2.6	11.8		
Sweden (clinical population)	1991–93 (Age 0–40)				7.3	33.8[a]		Lindberg et al. [51]
	1999–2001 (Age 0–40)				6.4	29.4[a]		
Denmark (clinical population)	1985–1990 (Age 5–30)		149			25.1[a]		Thyssen et al. [56, 57]
	1991–1996 (Age 5–30)		143			22.8		
	1997–2001 (Age 5–30)		116			20.2		
	2002–2007 (Age 5–30)		110			18.3[a]		
Denmark (clinical population)	1992–1997 (Age 2–30)		702			29.8[a]		Carøe et al. [48]
	1998–2003 (Age 2–30)		520			21.2		
	2004–2009 (Age 2–30)		428			19.6[a]		
Germany, Austria, Switzerland (clinical population)	1994 (Age 1–17)	80	161		7.5	29.2[a]		Schnuch et al. [54]
	1999 (Age 1–17)	95	185		5.3	19.5		
	2004 (Age 1–17)	81	125		8.6	16.0		
	2009 (Age 1–17)	90	133		6.67	14.3[a]		
Germany, Austria, Switzerland (clinical population)	2005–2006 (Age 1–17)		278			17.3[a]		Schnuch and Schwitulla [53]
	2007–2008 (Age 1–17)		239			15.1		
	2009–2010 (Age 1–17)		306			14.0		
	2011–2012 (Age 1–17)		328			11.6[a]		
United Kingdom (clinical population)	1999–2002 (Age 3–15)			114			20[a]	Vongyer and Green [58]
	2009–2011 (Age 3–15)			137			7.2[a]	
United Kingdom (clinical population)	1995–2004			500			8.8[a]	Smith et al. [55]
	2005–2014			500			4.8[a]	
Sweden (clinical population)	1992 (Age < 40)				7.3	33.8[a]		Fall et al. [49]
	2000 (Age < 40)				6.4	29.4		
	2009 (Age < 40)				6.1	23.3[a]		

[a]Denotes a significant ($p < 0.05$) difference over the time periods cited

role in raising awareness and avoidance of exposure to items causing nickel allergy and Ni ACD.

Since nickel allergy is a life-long condition (once you are allergic to nickel, you will always be allergic to nickel), the analysis of patch test results is only an indication of the number of people allergic to nickel, not the number of people having Ni ACD reactions. In order to understand the effectiveness of the regulations in Europe, the number of newly sensitised individuals should be evaluated. Assessment of the prevalence of nickel allergy in young people who would (theoretically) only have been exposed to low-nickel releasing items since the implementation of the regulations provides the best indication of the effectiveness of preventing nickel allergy. A number of studies have investigated patch test reactivity in children in Europe. As shown in Table 5.2, rates of nickel allergy have decreased significantly in almost every study. In addition to the observed significant decreases in prevalence of nickel allergy, a study in Denmark demonstrated a significant decrease in the strength of the patch test reactivity in nickel-allergic individuals [59].

It is interesting to compare the results in Europe following the regulation with the prevalence studies for similar years and age groups in North America, where no nickel regulation exists (adapted from Zug et al. [60]); see Table 5.3. Note that this high incidence approximately doubles in the data collations of the North American Contact Dermatitis Group (for the full age range) from the 1970s [61] through to the most recent data [62].

Reduction of the incidence of Ni ACD in already nickel-allergic individuals requires information on the number of Ni ACD reactions that are seen in patch test clinics, either in the form of case reports or number of relevant positive patch tests. Unfortunately, this data is not always recorded or easily accessible. A study by Smith et al. [55] provided information on patch test positive reactions and their relevance to the concurrent dermatitis for two different time periods. For 1995–2004, 44 out of 500 tested children (8.8%) had positive patch tests for nickel sulphate, but only three of these reactions were relevant to their existing dermatitis for which they were seeking treatment. The 2005–2012 data showed that 24 of the 500 tested children (4.8%) had positive patch tests for nickel sulphate, with only 7 of these 24 reactions being relevant to their existing dermatitis. The patch test prevalence to nickel significantly decreased, but given the low numbers of relevant reactions (and lack of presented statistics for relevance), the amount of change is not clear to assess a decrease in Ni ACD reactions.

Conflicting evidence exists on whether there has been a change in the association of nickel allergy and piercings following the EU nickel regulations. Mortz et al. [63] found a remaining significant association, while Jensen et al. [64] encountered a significant decrease in the association between piercing and nickel sensitisation. In countries where no regulation has been implemented, piercing is still a major risk factor for nickel allergy [65, 66].

5.2.4 Scope for Improvement

Although there is clearly a significant decrease in the prevalence of nickel allergy in Europe in the young population, the values still remain non-negligible. The sources of this continued induction of nickel allergy are not clear. Certainly there

Table 5.3 The prevalence of nickel allergy in North America in the twenty-first century

		# of patients tested			Positive to nickel (%)			
Country	Year	Male	Female	Total	Male	Female	Total	Reference
North America (clinical population)	2001–2004 (Age 0–18)			391			28.3	Zug et al. [60]
	2005–2012 (Age 0–18)			883			28.1	

is evidence that enforcement of the nickel restriction is of concern given the market surveys and case reports where high nickel-releasing items are documented to still be on the market [67–70]. In addition, a recent questionnaire-based study highlighted that Ni ACD reactions were primarily reported as associated with articles, such as ear piercings, specifically listed in the current EU nickel regulation [71]. These findings would suggest that these items may not be compliant with the regulation. For instance, according to the same report from the Danish EPA [71], several investigations show that up to 20% of articles are still positive to the nickel DMG test. Given the lack of available funding and human resources in many countries, along with the lack of requirement for enforcing this regulation under REACH, it is quite likely that products that are not compliant with the regulation remain on the market in Europe.

A less likely possibility is that the existing nickel release rate limits are not sufficiently low to prevent nickel allergy or Ni ACD reactions. However, this seems improbable given the type and amount of scientific data that has gone into the derivation of the current nickel release limits. Furthermore, nickel is known to be a weak allergen [6–8], with an elicitation threshold of 0.44 μg Ni/cm^2 (skin surface area) [72]. In addition, much work has been done to refine the protocols for measuring the nickel release rate by the CEN committees and related EN standards. Nevertheless, there remains the consideration of particularly susceptible subpopulations of individuals; this is an entire chapter in its own right and one where there remains an absence of consensus. Factors that should be kept in mind though include the need to consider the role of frequent low-dose exposure compared to less frequent but prolonged higher doses and the potential for filaggrin deficiency to elevate the risk of susceptibility to sensitisation (but not elicitation) [73, 74]. Indeed, although some factors such as psoriasis and atopic dermatitis appear unrelated to the acquisition of Ni ACD (where the presence of this allergic disease remains elevated), it is always necessary to keep an open mind regarding "current wisdom", potential causation, and the role of any regulatory or other actions which have the aim of reducing the morbidity.

While the release limit in the nickel restriction is not likely to be the cause of the remaining nickel allergy and Ni ACD reactions, the associated test method (EN1811) for measuring nickel release may play a role. The original EN1811 test method [25], included an adjustment factor of 0.1 that was applied to the results of the nickel-release test measurement to address difficulties in measuring surface area and intra-laboratory variability. Application of this adjustment factor meant that items could release as much as ten times the release limit and still be compliant with the nickel restriction. Improvements in the test methods were made, and the adjustment factor was replaced by an uncertainty adjustment in 2011, with the amendment in 2015 (EN1811:2011+A1 2015; [36], European Committee for Standardisation (CEN) 2015). This uncertainty adjustment resulted in nickel release rate limits (<0.35 μg/cm^2/week for post assemblies and <0.88 μg/cm^2/week for items intended for direct and prolonged skin contact) that much more closely approximate the nickel restriction limits (<0.2 μg/cm^2/week for post assemblies and <0.5 μg/cm^2/week for items intended for direct and prolonged skin contact).

It also may be possible that additional items should be included under the EU nickel regulation. In the recent study by the Ministry of Environment and Food of Denmark [71], keys were noted as being responsible for recent Ni ACD reactions. As they are not listed specifically in the EU regulation and they may not generally be considered as being in direct and prolonged contact by many people, this may be an example of an item that could be overlooked by the current EU nickel regulation.

5.2.5 Outstanding Questions

In addition to the question of why nickel allergy continues to be seen in the young population where a nickel regulation exists, the question of

what the clinical definition of the duration of prolonged contact needed to cause nickel allergy or Ni ACD remains. The current definition of prolonged contact, as approved by CARACAL, was based on a number of conservative assumptions. In addition, the data used was not necessarily relevant to nickel allergy and Ni ACD reactions observed in humans and associated with articles on the market that are responsible for causing these allergic reactions. An ongoing study involves patch testing nickel-allergic individuals for varying amounts of time, including those specified in the current CARACAL definition [75]. This study uses nickel-plated discs to represent types of materials in articles used by consumers that are most likely to trigger Ni ACD reactions. The results are expected to either confirm the exposure times currently noted in the definition of prolonged contact or better define what exposure times are needed for Ni ACD reactions. A report for this study is expected in mid-2017.

Another significant question is what the primary sources of nickel allergy and Ni ACD in children are. While ear piercing is certainly an ongoing source and concern, even children without pierced ears can become allergic to nickel. A retrospective study looking at data from the Ni ACDRG database is being initiated at the end of 2016 to identify what sources are associated with nickel allergy in children. This study is expected to be completed by the end of 2017 [76].

Finally, the question of the presence on the EU market of articles which are non-compliant with the EU nickel regulation remains. Data from a study in two locations identified that this was a problem in about one in six earrings purchased in Warsaw and London [69]. A larger survey of nickel release (EN1811 and DMG testing) of items that are currently covered under the nickel regulation, from a variety of price ranges and types of retailers in different countries, would help address this question. As females continue to be affected more than males, with the explanation being more use of pierced items and other jewellery by females, these items will be a particular focus. Such a survey is planned for 2017 to better understand the contribution of enforcement issues to the ongoing nickel allergy prevalence and incidence of Ni ACD [77]. Furthermore, a coordinated enforcement project (REF-4) was launched in 2016 at the EU level, in cooperation with member states, to check compliance with a number of REACH restrictions, including the one on nickel release in articles in direct and prolonged skin contact. The results are expected to be available in 2017. Such efforts to further improve enforcement and compliance with the existing EU nickel restriction are welcome and can give an important contribution to reduce the prevalence of nickel allergy and incidence of Ni ACD.

5.3 Chromium

5.3.1 Background

Potassium dichromate was already a key allergen on the original diagnostic patch test list of the International Contact Dermatitis Research Group (ICDRG) in 1974, a clear indicator that clinical experience had previously demonstrated that allergic contact dermatitis to chromium was one of the 20 most important skin allergens of the twentieth century [78, 79]. The frequency of positive reactions varied according to location but commonly approached, or even exceeded, 10% of consecutive eczema patients with contact allergy to the material (e.g. [61, 79, 80]). The sources of chromium allergy were already well known at the time—leather, cement, and a host of other industrial uses [79]. Almost 40 years later, the most recent textbooks of contact dermatitis detail a very similar profile [81, 82]. However, the most important source of exposure detailed in these (and many other) publications was cement. Building workers who developed allergic contact dermatitis via this route were well known to have a poor prognosis [79, 83]. Consequently, this was the primary target for legislative action to regulate the exposure to hexavalent chromium. Subsequently,

attention was turned to leather as a source of exposure, and legislation is also now in place for that material. All of this has been thoroughly reviewed relatively recently [84].

5.3.2 The Regulations

Within the European Union, a directive was introduced in 2003 which required that within 2 years, each member state would introduce legislation to limit the exposure to soluble hexavalent chromium (Cr VI) from cement to a maximum of 2 ppm [5]. It also required labelling to indicate the "shelf life" of product. That EU directive was itself superseded, but not changed, by the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation a few years later [85]. The relevant industry responded with the necessary actions (e.g. see review of [86]). Subsequently, the EU regulation has been updated also to restrict the release of Cr VI from leather products [4]. The effect of this is to try to ensure that leather articles coming into contact with the skin are not placed on the market if they contain Cr VI in concentrations ≥3 mg/kg (0.0003% by weight) of the total dry weight of the leather. This action was no doubt prompted by the observation of the importance of leather as a source of chromium allergy, even to the extent that it was implicated as a reason for the increase that occurred in Denmark many years after the implementation of national cement legislation in that country ([56, 57]; Carøe et al., 2010).

5.3.3 Evidence of Effectiveness

A key indicator of the likelihood of the success of the EU legislation had already been foreshadowed by the marked differences in the experience of workers involved in the construction of the Channel Tunnel, between the UK and France. In the UK workforce, two-thirds of those with exposure and occupational dermatitis (largely grouters) were patch test positive to potassium dichromate [87]. However, anecdotally, workers on the French side were largely unaffected (Richard Rycroft, personal communication), and it was already well understood that the addition of a small dose of ferrous sulphate to the wet cement could lead to a dramatic reduction in the frequency of chromate allergy [88]. That experience from Denmark demonstrated that "there was a statistically significant decrease in the prevalence of chromate allergy and hand eczema following the addition of ferrous sulphate". More recently, distinct evidence of a reduction in the frequency of chromium allergy in the German construction industry was reported [89]. However, it must be borne in mind that this last-mentioned publication reported a reduction in positive diagnostic patch tests from 43 to 29%, indicating, perhaps rather powerfully, that there is still distinct scope for improvement in the construction industry. The very latest and carefully conducted analysis from large occupational groups in the UK and France suggests that the impact of the Cr VI legislation in Europe has been to deliver an approximately 50% reduction in the incidence of disease [90]. Nevertheless, it is well worth noting that the legislation only has the chance to be effective if it is properly applied. The recent case of a 22-year-old Swedish concrete worker clearly demonstrated how important this is, as well as delivering a timely reminder of the risk of more chronic skin disease despite (apparent) removal from chromium exposure [91]. Finally, to counterbalance this relatively positive view of the effectiveness of the chromium legislation, it is of course quite possible that changes in the building industries, in the automation of process, and in the way materials are used have also made a significant contribution to the reduction in allergy.

Beyond the investigation of specific occupational groups, it is of course also possible to monitor the frequency of chromium sensitivity in the general eczema population, i.e. in those that undergo diagnostic patch testing, not least since potassium dichromate is in the baseline series and thus tested on every patient. Some of the most extensive data could be derived from the North American Contact Dermatitis Group, but in the context of evidence of the effectiveness of

legislation, this is of limited value, since there is no legislation in this region! However, it provides at least some background sufficient to advocate caution in the interpretation of other evidence—from 1970–1976 the frequency of positive reactions to potassium dichromate varied from 7.8 to 10.4% [61]. That rate was reduced to <2% in the 2011–2014 data (Warshaw et al., 2015; [92, 93]). This must be significant, but is it relevant? Probably not: the patch test concentration was lowered from 0.5 to 0.25% in the intervening period; industry practices, including the use of personal protection, may well have changed; referral practices that determine who is patch tested and with what are unlikely to have remained constant; sources of exposure will have changed. This is not to say that evidence of the effectiveness of legislation in the preceding paragraph is to be ignored, merely that care should be taken to ensure all variables are considered before drawing firm conclusions from routine patch test data. In this respect, it is valuable to examine the survey data recently published [84]. Apparent downward trends in the rates of positive reactions to potassium dichromate seen in an individual clinic (Gentofte), in Europe and in North America, are quite comparable, even though no legislation has been enacted in the last-mentioned location (see Fig. 5.1, which shows a 30-year period of screening with potassium dichromate sensitivity in the North American region compared to relevant European data). In reality, it is the upward trend in Asia, starting from an already higher base, that is truly worrisome [84, 94].

5.3.4 Scope for Improvement

A first action to take must be to encourage introduction of the European type of legislation into other geographic locations. For example, a recent review from Israel demonstrates a clear need for such regulation in that country [95]. Similar calls from other countries are easily identified (e.g. [94, 96–98]). There is little doubt that all nations should adopt this good practice, although it might reasonably be argued that the cement industry itself should take the lead rather than wait to be

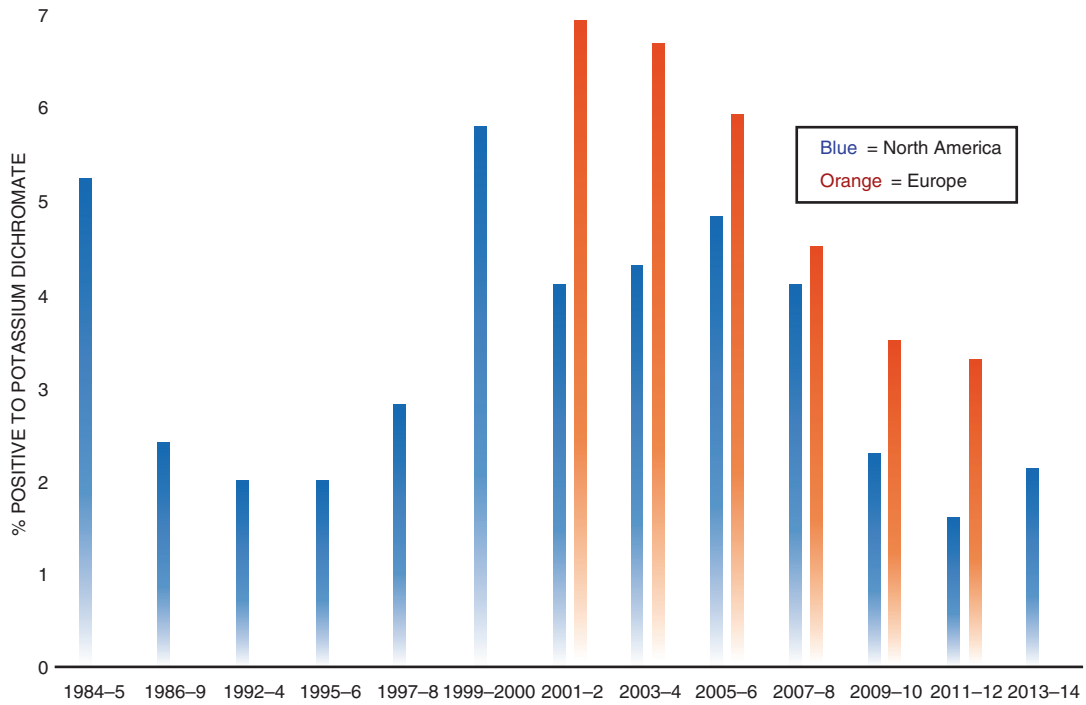

Fig. 5.1 The prevalence of Cr VI-positive reactions in Europe versus North America

compelled. Indeed, some nations have done precisely this.

Beyond the limitation of chromium exposure from cement, it is necessary further to limit exposure from other sources. Apparently to that end, the EU will introduce a ban on the use of hexavalent chromium salts for the plating of decorative objects during 2017 (see http://nomorehex.org/LEGISLATION/EU-MANDATE). However, this actually is an unintended consequence, since the legislation appears to be based on the carcinogenic properties of these salts, not on their potential for skin sensitisation. Chrome plating has not proven an important source of contact allergy in consumers but is relevant in the occupational environment. A similar logic applies to the restriction for packaging (not a frequent source of allergy), which limits the total content to a maximum of 100 ppm Cr VI [99], as well as for electrical/electronic equipment for which the substitution of safer alternatives to Cr VI (and several other toxic metals) has become a requirement (see http://ec.europa.eu/environment/waste/rohs_eee/index_en.htm). Thus, real improvement would necessarily only really come from the identification of important continuing sources of chromium allergy (as was done for leather), followed by appropriate action and monitoring.

5.3.5 Outstanding Questions

In a sense, the challenges faced for chromium allergy are similar to those found with many causes of allergic contact dermatitis: namely, to identify the key sources of exposure, particularly those that are relatively obscure (e.g. [84]). The second question is how to demonstrate the effectiveness of any particular legislative action, set against the background of changing work patterns, varying clinical referring and testing practices, and so on. Finally, whereas for nickel the DMG spot test (despite many limitations) provides a handy tool to detect the presence of the allergen, nothing truly similar exists for hexavalent chromium salts; recent development of a diphenylcarbazide (DPC) spot test has the potential to assist in reducing the morbidity of the disease and could be critical in helping to eliminate the chronic nature of chromium eczema [100]. However, the fact that the test needs to be kept frozen renders it somewhat less user-friendly, so only time will tell whether it functions to deliver similar benefits to the DMG test.

5.4 Concluding Remarks

Decreasing the prevalence of skin sensitisation to common allergens to a negligible or even to a socially acceptable level requires adequate and relevant scientific input into regulatory activities and communications with and between stakeholders. Through compliance with the resulting regulatory restrictions and sufficient stakeholder communication, significant and acceptable reduction in the prevalence of skin sensitisation to common allergens can be achieved. The complexity of monitoring the incidence/prevalence of the disease should not be underestimated but, as experience has shown, without appropriate monitoring, regulation alone may have little, if any, impact [78]. The experience with nickel and Cr VI provides an important learning opportunity that should help with the mitigation of other causes of allergic contact dermatitis, as well as with continuing efforts to manage other sources of exposure to these two allergenic metals.

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Part II

Metals, Skin, and the Immune System

6 Deposition of Metals on the Skin and Quantification of Skin Exposure

Klara Midander

6.1 Metals on the Skin

The skin comes into contact with metal many times a day, throughout life. The skin is exposed every time we touch metallic objects or use household chemicals and consumer products containing metals. Also, metal-containing particles from the surrounding environment might end up on the skin. Within some professions, such as metalworkers, locksmiths or cashiers, the total exposure to metals can be high (Table 6.1). To many of us, daily skin exposure to metals involves many short but frequent contact events with metal of various forms. Altogether, these contacts will potentially contribute to metal deposition onto the skin at the same time that we may contaminate other surfaces by redeposition of metals via touch. In contrast to the potentially higher occupational exposure, skin exposure to metals from normal daily activities can often be described as a continuous, low-dose exposure of a diffuse nature.

In the context of contact allergy, the metal skin dose is key. For the manifestation of allergic hypersensitivity in the form of eczema, direct skin contact with the metal is required. In fact, the dose is all-out inseparable from the *amount* of metal as well as the *area* of contact (μg/cm^2) [1]. The duration and the frequency of contact are important characteristics of exposure [2, 3]. Moreover, the condition of the skin controls both the size of the dose as well as the fate of metals on the skin [4] (Fig. 6.1).

6.1.1 Exposure

When a metal-containing material comes into contact with the skin, the material surface is affected by sweat present on the skin surface. This will result in the release of metal from the material due to dissolution, corrosion and/or wear processes [5, 6]. The extent of metal release depends on specific conditions at contact related to the skin, material and environment. Such conditions include the duration and frequency of contact, temperature, pH and the presence of sweat, sebum and other skin components, as well as material properties such as type of material (pure metal, alloy, other materials with metal-containing surface coating or metal incorporated in the matrix) and the condition of the material surface [6–8].

6.1.1.1 Material Properties

Properties of the material in contact with the skin are of the utmost importance to what metals and at what quantities metals end up on the skin. We are surrounded by metallic materials in our daily lives, and a modern society is dependent on a vast

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Table 6.1 Examples of studies using skin sampling methods to quantify the metal skin dose in occupational settings as well as consumer and experimental exposures

Method for quantification	Metals quantified	Number of people	Reported skin doses	Study environment [sampling period]	Study
Occupational skin exposure					
Acid wipe sampling	Ni	$n = 6$	Index 0.047–0.29 μg Ni/cm^2 Palm 0.0097–0.037 μg Ni/cm^2	Ni allergic patients with occupationally induced dermatitis [120 min]	Jensen et al. [46]
Acid wipe sampling	Ni	$n = 18$	Thumb/index/middle[a] 0.092–0.90 μg Ni/cm^2(carpenter) 0.42–1.26 μg Ni/cm^2(locksmith) 0.017–0.83 μg Ni/cm^2(cashier) 0.011–0.045 μg Ni/cm^2(secretary) Palm 0.025–0.11 μg Ni/cm^2(carpenter) 0.11–0.32 μg Ni/cm^2(locksmith) 0.0050–0.14 μg Ni/cm^2(cashier) 0.0030–0.016 μg Ni/cm^2(secretary)	Carpenters ($n = 4$, 150–180 min), locksmiths [$n = 3$, 110–120 min], cashiers [$n = 7$, 10–185 min] and secretaries [$n = 4$, 60 min]	Lidén et al. [47]
Acid wipe sampling	Ni, Co, Cr	$n = 24$	Thumb/index/middle 0.021–15 μg Ni/cm^2 0.0025–4.5 μg Co/cm^2 0.0015–0.58 μg Cr/cm^2 Palm 0.0033–5.3 μg Ni/cm^2 0.00054–0.26 μg Co/cm^2 0.00069–0.085 μg Cr/cm^2	Workers in production industry (turbine and space propulsion components) [1.7–2.3 h]	Julander et al. [48]
Acid wipe sampling	Ni, Co, Cr	$n = 13$	Index 0.0011–0.27 μg Ni/cm^2 0.0011–1.6 μg Co/cm^2 0.0010–0.19 μg Cr/cm^2	Workers in dental technician laboratory [1.75–2.8 h]	Kettelarij et al. [45]
Finger immersion	Ni	$n = 44$	Index 0.002–0.065 μg Ni/cm^2 (shop assistants) <0.0009–0.038 μg Ni/cm^2 (department store workers) <0.0009–0.0018 μg Ni/cm^2 (hairdressers) <0.0009–0.0034 μg Ni/cm^2 (bar staff) 0.0079–1.3 μg Ni/cm^2 (nickel refinery workers) 0.020–7.2 μg Ni/cm^2 (nickel platers)	Nickel platers and refinery workers, hairdressers, bar staff, shop assistants and departments store workers [regular work shift]	Staton et al. [37]
Ghost wipes	Ni	$n = 26$	Index 0.24–18 μg Ni/cm^2 (break 1) 0.30–42 μg Ni/cm^2 (break 2) 0.81–11 μg Ni/cm^2 (after shift) Palm 0.045–230 μg Ni/cm^2 (break 1) 0.064–57 μg Ni/cm^2 (break 2) 0.52–19 μg Ni/cm^2 (after shift)	Metal refinery workers [tea break, lunch break, after shift]	Du Plessis et al. [35]
Wash 'n Dri® wet wipes	Ni, Co, Cr	$n = 41$	Hands (palm and back)[b] 1.7–488 μg Ni 4.1–4285 μg Co 0.5–101 μg Cr Neck[b] 0.3–137 μg Ni 0.5–693 μg Co 0.3–39 μg Cr	Hard-metal workers [mid-shift, end of shift]	Day et al. [49]

Table 6.1 (continued)

Method for quantification	Metals quantified	Number of people	Reported skin doses	Study environment [sampling period]	Study
Consumer skin exposure					
Acid wipe sampling	Ni	$n = 3$	Middle finger 0.28–1.2 μg Ni/cm^2 Palm 0.30–1.7 μg Ni/cm^2	Workout with free weights [60 min]	Gumulka et al. [50]
Experimental skin exposure					
Acid wipe sampling	Ni	$n = 3$	Thumb + index + middle[c] 1.0–2.6 μg Ni/cm^2 Palm 0.05–0.75 μg Ni/cm^2	Skin deposition of Ni from coin handling [1 h]	Lidén et al. [51]
Acid wipe sampling	Ni	$n = 6$	Thumb + index + middle 0.32–21 μg Ni/cm^2	Skin exposure from handling Cu-Ni or Ni-plated coins [1 h]	Julander et al. [5]
Acid wipe sampling	Co	$n = 5$	Thumb + index + middle 0.03–1.6 μg Co/cm^2	Skin exposure from manipulating hard-metal discs [30 min]	Midander et al. [9]
Acid wipe sampling	Ni	$n = 5$	Index 0.024–4.7 μg Ni/cm^2 (3 s touch) 0.017–9.1 μg Ni/cm^2 (15 s touch) 0.050–7.2 μg Ni/cm^2 (30 s touch)	Short skin contact with Ni-containing alloys [3, 15 and 30 s]	Erfani et al. [6]

[a]Skin dose at any of the three fingers
[b]Amounts are geometric mean values for participants in different work areas
[c]Mean value of doses measured on the three fingers

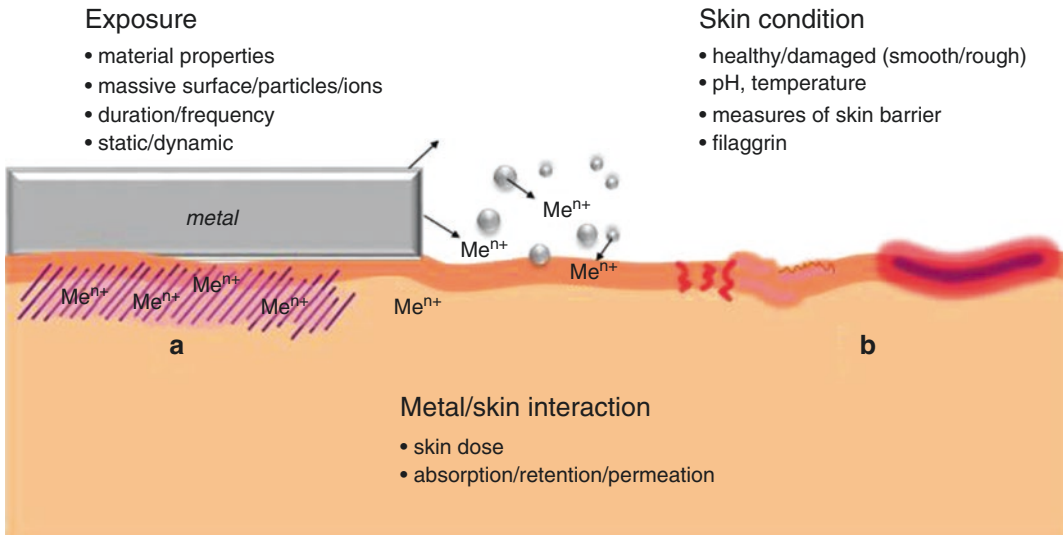

Fig. 6.1 Metal deposition on the skin is described by the characteristics of exposure and the condition of the skin, as well as the interaction between metal and the skin. (**a**) The metal skin dose is decisive for any effects of metal skin exposure. (**b**) The skin condition (i.e. smooth and moist or rough, dry, eczematous, scaly with fissures/ridges) plays an important role in the contact event causing a dose of metals to be deposited on the skin. Also, the skin condition influences the fate of metals on the skin since it affects the barrier properties and hence the absorption/retention/penetration of metals in/through the skin

variety of engineered alloys and metal-containing materials. In order to grasp which properties of a material are decisive in contact with the skin, the chemical composition of the materials serves as a starting point, and any content of a sensitising metal should be regarded as a hazard in the context of contact allergy. However, a metallic surface in the abundant atmosphere is always oxidised to some extent and, especially for alloys, the composition of the surface does not necessarily reflect the composition of the bulk material. The fact that it is the material surface, with its surface oxide, that primarily comes in contact with the skin is key for understanding which metals will deposit on the skin from a touch or shorter contact event. The release of metal from the surface in contact with sweat on the skin is hence regarded as chemical dissolution of the surface oxide. In the case of prolonged skin contact, the contribution by corrosion-induced release of metal from the material will also have an impact on metal deposition onto the skin.

6.1.1.2 Form of Metal

The form (surface, particles, ions) of the metal or metal-containing material is also of importance for the outcome of skin exposure in the sense of metal release and the potential skin dose from contact. For example, it is well known that nanoparticles release more metal compared to a massive material due to the larger surface area of nanoparticles and the higher reactivity of small particles (higher surface atoms/bulk atoms ratio). This is expected to have consequences for the exposure of the skin and the possible local and systemic effects from such exposure, since metal nanoparticles are increasingly used in many consumer products.

6.1.1.3 Duration and Frequency

The duration and frequency of skin contact with metals are important descriptors of exposure. Traditionally, the prolonged contact scenario has been associated with the manifestation of contact allergy to metals, in particular to nickel. The importance of the short and repetitive character of nickel skin exposure in the induction of an allergic response is demonstrated by the correspondence between the elicitation threshold with closed patch testing (the clinical tool for diagnosis of contact allergy) and the accumulated dose by repeated open application tests (ROAT). The dose-response relation for the accumulated ROAT dose at 1, 2 and 3 weeks was similar to the single dose-response patch test [2]. It has also been shown that metal release rates (the speed of which metal ions are solubilised) in sweat are initially high but decline with time [5, 9].

6.1.1.4 Static and Dynamic Contact

Physical conditions at contact such as static or dynamic force applied in a grip or sliding touch are parameters that are rarely considered nor understood in the context of skin exposure to metals [6]. However, processes of friction and wear are a natural part of our daily use of metallic materials, both professionally and as consumers, and have been experimentally studied for some materials and items of relevance for contact allergy [5, 9].

6.1.2 Skin Condition

The condition of the skin is vital, maintaining homeostasis and protecting the body from the harsh environment. However, for many people with chronic eczema or skin disease such as atopic eczema, allergic contact dermatitis or psoriasis, these vital functions are not working optimally.

6.1.2.1 Healthy and Damaged Skin Barrier

The sensation from a touch of a hand can present most of the physiological conditions of the skin: warm, soft, smooth, moist, cold, dry, hard or rough. All of them can actually be categorised into different degrees of temperature, topography and hydration of the skin surface. Also, skin elasticity, the topography of the counter surface and the adhesion between the skin and surface are important for the tactile experience of a material. Altogether, these different factors are of importance to metals on the skin since they will affect the quantity of a skin dose from touch.

The skin's condition can be described by several physiological measures of barrier properties including skin hydration, evaporation, resistance/inductance/capacitance, temperature, pH and various measures of topography [10, 11]. Healthy skin is characterised by sufficient hydration of the stratum corneum, which makes skin feel smooth and soft. In damaged or dry skin, the barrier properties are affected, with a reduced degree of hydration (monitored by measuring the capacitance over the stratum corneum) [12]. Also, the passive diffusion of water through the skin (measured by monitoring transepidermal water loss) reflects the permeability of the stratum corneum [10]. Both hydration and evaporation are related to the ability of the skin to maintain a good hydration balance, which in turn is affected by skin temperature.

6.1.2.2 Filaggrin

From a dermatological point of view, 'dry skin' is often characterised by marked hyperlinearity on the surface of the palms and fingertips. This condition can be of a genetic nature with a loss-of-function mutation in the filaggrin gene that is responsible for the pH and buffering capacity of the skin. It also affects skin hydration by lowering the amount of natural moisturising factors (different amino acids) that provide moisture in the stratum corneum [13, 14]. Filaggrin deficiency is relatively common in Northern European populations (approximately 10% have one of the four most common mutations); hence, the filaggrin status in research persons is of importance as an additional factor to other skin physiological measures [14].

6.1.3 Metal/Skin Interaction

In contact allergy, the skin is the target organ when subjected to a skin dose of sensitising metal. It is not the penetration through the skin but the uptake of metal into the epidermis and the availability to antigen-presenting cells that is considered to be of relevance for sensitisation and elicitation. Hence, the residence time within the skin is of great importance and depends both on the transport of metal into and/or through the skin layers, as well as the outward transport of old and dead skin cells.

6.1.3.1 Absorption, Retention, Permeation

For most sensitising metals, permeation through the skin is limited, while it was shown that a depot of nickel in the stratum corneum was built up during 24 h when single doses of nickel were applied on the skin in various concentrations [15]. The concentration-depth profile of nickel in the skin was in this case obtained by tape stripping the skin at the application sites and a following analysis of tape strips for metal content. It was found that permeation rates depended on the counterion, that permeation rates increased with increasing the applied concentration and that diffusion rates changed over time. Moreover, the skin status may be important, assuming that metal ion permeability is higher in damaged skin than in normal skin. Also, the anatomical site plays a crucial role [4]. It was shown that reactivity to nickel in nickel allergic subjects was higher when the skin was pretreated with irritants and that allergic reactivity was increased on skin sites with previous nickel contact dermatitis [3, 15, 16]. The turnover time of the stratum corneum and of the epidermis have been estimated to be 2 and 4 weeks, respectively [17].

6.2 Quantification of Skin Exposure to Metals

Skin exposure to metals can be assessed by screening various sources, with measurements taken in the outer environment, at the skin surface, in the skin layers and through monitoring biomarkers of systemic exposure via the skin route. There are direct methods to measure exposure, as well as methods and models that function as experimental proxies for skin exposure.

6.2.1 Sources of Exposure

Potential sources of exposure in the surrounding environment can be assessed in several ways. One approach is to perform a market

survey and screen items of relevance for skin contact with sensitising metals. The approach has, for example, been implemented in studies with the aim to investigate compliance with legislative restrictions of nickel in various products [18–24]. Different methods of detection can be used in assessing the sources of exposure. They all have advantages and limitations and can preferably be used in combination to elucidate the different properties of materials in contact with the skin.

6.2.1.1 Spot Tests

Screening for the presence of nickel and hence potential nickel release from surfaces in contact with the skin can be performed by using the dimethylglyoxime (DMG) test. The DMG test (also called the nickel test) is a colorimetric semi-quantitative method to detect the release of nickel ions from a surface that is rubbed for 30 s with a cotton-wool stick moistened with the DMG test reagent solution. If nickel ions are released from the surface subjected to sampling, the reagent solution on the cotton-wool stick turns pink [25]. Similar tests for the detection of cobalt and chromium are available; however, the gathered experience with those is relatively limited. For example, semi-quantitative judgement of results has not been validated, and the occurrence of interference with other metals/false-positive reactions has not been completely clarified [26, 27].

6.2.1.2 Release Tests in Artificial Sweat

Release of metal from surfaces can also be assessed in experimental immersion experiments, through the exposure of a material or item to artificial sweat. This is the concept of the EN1811 standard reference test method, a compliance test of nickel release from materials with intended use in prolonged contact with the skin. Compared to the test matrix of spot tests (i.e. a chemical reagent solution), artificial sweat is relevant for real-world skin exposure in the sense of ion strength and pH. The results of a release test in artificial sweat at defined conditions mimicking skin contact may be considered a 'worst case scenario of exposure' under the assumption that all the nickel released from a material surface in contact with the skin will deposit onto the skin [28]. Release tests in artificial sweat have been used to assess various materials as sources for skin exposure in the context of contact allergy and dermatitis [5, 9, 29–31].

6.2.1.3 Analysis of Chemical Composition

Elemental analysis of the chemical composition of materials that constitute sources of hazardous skin exposure to metals can be assessed in various ways. A relatively common method is the use of a hand-held x-ray fluorescence spectrometer, which provides results on chemical composition based on the detection of secondary fluorescent x-rays emitted from excited atoms in the material. The instrument provides quantitative and also qualitative data on chemical composition. The energy of the instrument x-ray source limits the range of elements that can be detected. It should also be stressed that this is not a surface-sensitive method and that the information depth of the XRF analysis rather reflects the bulk composition of materials (while it is the material surface that normally comes in contact with the skin). The analysis of materials, by XRF or other more sensitive spectroscopy techniques for the assessment of material and surface properties, can preferably be included in studies of the hazardous skin exposure to sensitising metals [5, 6, 9, 32].

6.2.2 Assessment of Metals on the Skin

The assessment of potential sources of skin exposure always provides an indirect measure of skin exposure that in fact can be assessed by direct measurement of metals on the skin

surface and/or in the skin layers. Several non- and semi-invasive sampling methods exist. Generally, the methods for detection and quantification of metals on the skin are based on (1) removal of the metals on/in the skin, (2) sampling a surrogate for the skin or (3) visualisation of the metal on the skin [33].

6.2.2.1 Skin Sampling for Quantification of Metal Skin Dose

The amount of metal (μg) on a defined area of skin (cm^2), the metal skin dose (μg/cm^2), can be quantified by removal of the metal from the skin surface, followed by chemical analysis of the sample. A common approach is to use a wipe for the skin sampling. Conventional wet wipes or ghost wipes as well as wipes moistened with diluted acid (1% HNO_3) have been used to quantify the metal skin dose in skin areas typically 2–10 cm^2 in size [34, 35]. Another way to remove metals from the skin is through rinsing or cleaning the skin, such as with immersion into water of a particular finger that was exposed [36, 37]. Bag rinsing of the entire hand has not been used for the quantification of metals on the skin, but could be adopted for this purpose by the use of a suitable solvent as the washing media (1% HNO_3 or water) [38, 39]. The above-mentioned methods have been implemented in several exposure studies, both occupational and consumer exposure, as well as in studies of experimental skin exposure (see examples in Table 6.1).

Tape stripping is another technique that is used to remove metals from the skin. Often, samples intended for quantification of the metal skin dose are collected by 3–10 consecutive tapes that collect the dead skin cells of the outer stratum corneum, and results will therefore only reflect the surface dose [Multi-analytical quantification of metal skin dose, Midander et al., in preparation]. By consecutive tape stripping (20–30 tapes), the skin cells of the epidermis are removed; hence, chemical analysis of the individual tape strips provides some information on the concentration gradient of metal in the outer skin layers (retention of metal/depot-formation) [40]. In a sample collected by punch biopsy (a dermatological method for invasive removal of the skin), the metal content in the entire skin sample or in parts of split skin can be quantified. This is rarely done in vivo but is often applied as a part of the analysis in experimental studies of skin uptake [41].

6.2.2.2 Alternative Techniques to Assess Metal Skin Exposure

Skin exposure to metals can be assessed by analysis of samples from exposed skin surrogates such as patches/Band-Aids placed on the site of interest (on clothes or under clothes directly onto the skin) [42]. Also, visualisation of metals on and in the skin can be used to demonstrate skin exposure. To visualise occupational exposure to nickel on the skin, hand imprints using the DMG test reagent solution have been used [25]. In order to detect nickel on the skin, the DMG test has been used directly onto the skin, even for semi-quantitative comparison of the nickel skin dose (Fig. 6.2, left) [32, 43].

State-of-the-art spectroscopy techniques have also been explored, in particular for the visualisation of experimental exposure to metal nanoparticles on/in the skin [44]. Also, traditional monitoring of biomarkers for exposure, in this case metal concentrations in the blood/urine, serves as a measure of exposure to metals. However, systemic exposure to metals via the skin route is generally difficult to distinguish from exposure via the airways or the gastrointestinal route [45]. Naturally, the clinical manifestations of skin exposure to sensitising metals are a measure of skin exposure, and the serial dilution patch test method can be implemented in studies of reactivity to varying skin doses of sensitising metals [1].

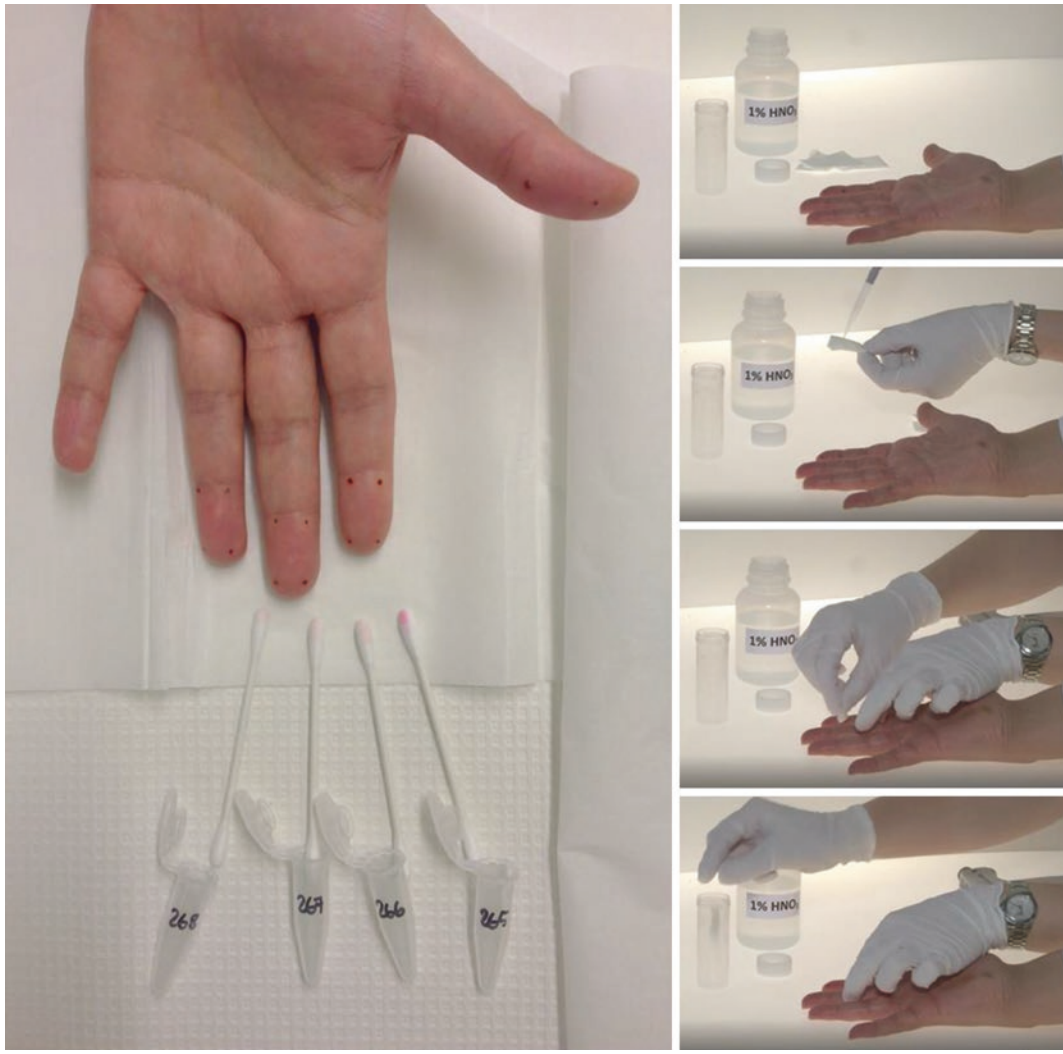

Fig. 6.2 The use of the dimethylglyoxime test to detect nickel on the skin (*left*). Sampling of metals from the skin surface by acid wipe (*right*)

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Penetration of Metals Through the Skin Barrier

7

Francesca Larese Filon

7.1 Introduction

The skin is a route of entry for substances that come in contact with the stratum corneum and has an important role for the penetration of haptens, which can induce contact sensitization and allergic contact dermatitis. In addition, toxic substances (detergents, acid, soaps, etc.) can act as irritant factors on skin layers, increasing skin permeation of other products, such as haptens. Other substances can pass through the skin, reaching the dermis and, from there, the general circulation, inducing the potential for systemic intoxication.

Skin exposure to metals can happen during contact with metal objects, jewels, coins, or leather that can release metals such as nickel, chromium, cobalt, or palladium, particularly when in contact with sweat [1, 2]. New tissues have been made using silver nanoparticles and silver can also penetrate the skin [3], although urinary levels of silver in one study did not increase after exposure [4], meaning that the applied dose was not sufficient to cause systemic involvement.

Many workers, such as mechanics, solderers, electroplaters, miners, etc., are exposed to different kinds of metals or metal salts. Moreover, an environmental exposure exists to platinum group metals (platinum, rhodium, and palladium) which are released into the atmosphere by vehicle exhaust catalysts [5].

Metals in contact with the skin can be absorbed, reaching the viable layers of the epidermis and sometimes the dermis and general circulation. In general, skin permeation of metals has been underestimated, and much attention has focused only on local effects, as some metals are the principal cause of allergic contact dermatitis, such as nickel, chromium, palladium, and cobalt. Contact with metal objects and jewelry causes metallic ions to be released, which is enhanced by synthetic sweat [2, 6]. Metallic ions or their salts pass through the stratum corneum and reach the viable epidermis, where "antigen-presenting cells" are present and can initiate the type 4 Gell and Coombs sensitization process. Subsequently, metals can penetrate to the dermis and reach the systemic circulation in very low amounts. While sensitization can happen with extremely low doses, systemic intoxication requires high metal concentrations that are unlikely to occur with exposure to intact skin.

In skin penetration, a crucial aspect is the integrity of the skin barrier. Damaged skin, characterized by fissures, scaling, or desquamation, can increase metal skin absorption more than

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100–1000 times, and, for that reason, irritant contact dermatitis must often be considered the first step toward allergic contact dermatitis.

Finally, we consider the term "penetration" when the applied substance reaches the skin and "permeation" when a substance passes through the skin.

7.2 Route of Skin Permeation

Chemicals can be absorbed through the skin via different pathways [7, 8]:

1. The intercellular route, with partitioning into the lipid matrix
2. The intracellular route, for substances that can enter the cells
3. Through sweat glands and hair follicles [9]

Hair follicles can act as a shunt, increasing the penetration and absorption of topically applied substances [10–12] and nanoparticles (NPs) [13]. Hair follicles can also be considered a reservoir for penetrating chemicals and nanoparticles, since substances stored there can diffuse to the surrounding spaces, cross the capillary walls, and even reach the circulatory system [14].

Skin diseases, such as irritant contact dermatitis and atopic eczema, can increase the risk of hapten penetration, leading to a possible sensitization [15, 16].

Skin exposure to irritant compounds can enhance penetration likely due to disruption of the stratum corneum, either by means of protein denaturation agents, such as detergents, or through lipid extraction from the stratum corneum by means of solvent agents [17, 18].

7.3 Factors Involved in Skin Permeation

The skin can be considered a barrier membrane in which Fick's laws of diffusion are applicable and factors involved are summarized in Table 7.1. The involved area, time of contact, gender, differences in skin thickness, hair follicle density, blood flow, age, mechanical flexions for nanoparticles [27, 30], and systemic diseases may all influence the skin barrier function [31, 32].

7.4 Skin Absorption Studies

7.4.1 In Vitro Data on Animals and Human Skin

The approach to studying metal skin absorption can be in vitro, using Franz cells [33] with human or animal skin, that permits the definition of flux through the skin and the lag time (time in which the flux starts to be constant). These studies are widely used to evaluate drug permeation through the skin, and results can assist understanding of the skin absorption of chemicals [34] but need to be conducted following guidelines, i.e., using at least two donors to reduce variability, which is considerable between donors. However, the permeability coefficient measurements have a mean intraindividual coefficient of variation of approximately 40% [35], and an interindividual variation of about 70% [36]. Hostýnek [29] and Loth [37] suggested that these variations are related to differences in the lipid domain of the stratum corneum and that these in vitro studies reflected in vivo conditions.

Despite the wide variability, Franz cell results permit us to determine the amount of permeation of a substance, the time needed for permeation, and the amount of metals inside the skin. In Table 7.2, some results related to metal penetration studies performed using metal powders in micron or nanosize ranges are summarized. Many other data are available for metal salts that have an increased potential for skin penetration due to their chemical characteristics [23, 44–47].

A flux through the skin has been demonstrated for all metals tested (Ni, Co, Pd), except for chromium which is probably strongly bound to skin proteins [48]. In general, flux is very low and in the range of ng/cm^2/h and has been shown to

Table 7.1 Factors involved in skin absorption

Dose
The applied dose can influence skin absorption in variable ways. In some cases, an increased dose can result in increased permeation, but under other conditions, skin absorption can be negatively influenced. For example, chromium skin levels in the skin increased with increasing concentrations of applied chromium salt up to 0.034 M Cr [19]. Conversely, mercuric chloride skin absorption was shown in the guinea pig to reach a maximum at 16 mg hg/ml and decreased to non-detectable levels with increasing concentrations [20].
Ions released (counter ion)
Sweat can increase ion release from metal objects, thus increasing skin permeation [21]. Different nickel salts penetrate the skin in different amounts, and the phenomenon is influenced by occlusion [22].
Area of the skin contaminated
Anatomical site
Skin penetration varies markedly at different body areas. Hostýnek in 2001 [22] suggested a decreasing trend of penetration from scrotum-forehead-postauricular-abdomen-forearm-leg-back. Differences are related to skin thickness and to intercellular lipid composition.
Thickness of the skin reduces skin absorption
Duration of skin contact increases permeation and penetration
Vehicles
Solvents and detergents can increase permeation due to their irritant effects, and different formulations can change skin absorption [23, 24].
Temperature can increase skin permeation
Humidity can increase sweating that, in general, increases permeation
Blood flow can increase skin permeation
Physical activity can increase skin permeation
Gender and race affect skin penetration and permeation as, in general, female skin is thinner and stratum corneum impairment more frequent
Age affects skin penetration, which is inversely related to age
Hair follicle and sweat gland density
This route of entry is extremely important because it is faster than intercellular and intracellular routes. For nickel salts, 25–46% of the dose can be inside follicles [25]. The "follicular route" can be considered the most efficient [13] for nanoparticles. Moreover, electrolytes can also be excreted through hair follicles, and for some elements such as iron (II), zinc(II) and copper (II), sweat can be considered an important pathway [26].
Mechanical flexion of the skin can increase penetration and permeation of nanoparticles [27]
Skin condition
Skin barrier impairment increases metal penetration. Nielsen et al. [28] demonstrated that nickel hypersensitivity develops quickly on nickel exposure of irritated skin compared to application on intact skin.
Characteristics of the substance
Molecular weight is inversely related to permeation.
Valence: Trivalent chromium is less permeable than hexavalent chromium, and cream containing iron sulfate can reduce chromium skin penetration, changing the valence of chromium [29]. This aspect is probably due to the strong binding of trivalent chromium to epidermal proteins.
Octanol/water partition influences skin absorption.
pH can modify the skin absorption.
Storage inside the skin
Nanoparticles in contact with the skin can be stored inside follicles, and from there ions can diffuse into the dermis [13]. Some metals can be bound to skin proteins, such as chromium (III), silver (I), mercury (II), aluminum (III), and nickel (II), as well as the metalloid arsenic (III) [23, 29].

increase 10–100 times in skin damaged with a needle. Particle size influences absorption, and metal NPs represent a higher potential for penetration and permeation than metals in micron size, considering the lower dose applied in nano-form [49, 50]. Lag time ranges between 1 and 14 h and is generally lower for NPs (Pd and Ni), with the exception of cobalt [51].

The application of chromium in metal powders did not cause a permeation flux through

Table 7.2 Permeation studies of sensitizing metals

Metal	Flux μg/cm²/h (mean ± SD)	Lag time (h)	Donor dose mg/cm²	Metal into the skin (μg/cm²)	Skin	Reference
Ni 2.3–3 μm	0.0165 ± 0.00036	14.56 ± 0.56	15.2	–	Human intact	Larese et al. [6]
Ni 2.3–3 μm	–	–	23	82.3	Human intact	Larese et al. [38, 39]
Ni 2.3–3 μm	–	–	23	131	Human damaged	Larese et al. [38, 39]
Ni NPs 77 nm	0.0017 ± 0.0006	6.0 ± 1.4	0.6	9.67 ± 2.70	Human intact	Crosera et al. [40]
Ni NPs 77 nm	0.30 ± 0.12	6.6 ± 0.8	0.6	29.2 ± 11.2	Human damaged	Crosera et al. [40]
Pd NPs 10.7 nm	0.005 ± 0.003	4.8 ± 1.7	0.6	0.69 ± 0.36	Human intact	Larese et al. [41]
Pd NPs 10.7 nm	0.057 ± 0.030	4.2 ± 1.6	0.6	0.93 ± 0.41	Human damaged	Larese et al. [41]
CoO4NPs 17 nm	Nd		0.6	16.8 ± 10.98	Human intact	Mauro et al. [42]
CoO4NPs 17 nm	0.002 ± 0.002	4.3 ± 2.1	0.6	12.3 ± 6.18	Human damaged	Mauro et al. [42]
CoNPS 80 nm	Nd	Nd	1	4.35 ± 1.36	Human intact	Larese et al. [43]
CoNPS 80 nm	0.076 ± 0.049	2.8 ± 2.1	1	12.8 ± 3.8	Human damaged	Larese et al. [43]
Co 2 μm	0.123 ± 0.0054	1.5 ± 5 0.71	15.2	–	Human intact	Larese et al. [6]
Co 2 μm	–	–	23.9	29.6 (median)	Human intact	Larese et al. [38, 39]
Co 2 μm		–	23.9	48.7 (median)	Human damaged	Larese et al. [38, 39]
Co 2 μm	0.55 ± 0.33	–	15.9	12.3 ± 5.4	Human intact	Larese et al. [21]
Co 2 μm	76 ± 49.3	–	15.9	Nd	Human damaged	Larese et al. [21]
Cr	Nd	–	15.2	Nd	Human intact	Larese et al. [6]
Cr < 10 μm	Nd	–	23	14.4 (median)	Human intact	Larese et al. [38, 39]
Cr < 10 μm	Nd	–	23	62.1 (median)	Human damaged	Larese et al. [38, 39]

Studies were performed using Franz cells with the application of metal powders or nanoparticles to full-thickness skin
Nd not detected, – data not available

the skin, but this metal can be found inside the skin in higher amounts when the skin is damaged [6]. The application of $K_2Cr_2O_7$ instead resulted in the significant permeation of this metal, reaching a flux of 7.29 μg/cm²/h and confirming that a metal's salts can pass in higher amounts through the skin. The lag time was around 12 h [6].

7.5 "Disappearance Measurements"

This method, which involves the application of radiolabeled metals followed by evaluation for the disappearance of radioactivity on the skin, demonstrated many years ago that metals can pass through the skin [52–54].

7.6 In Vivo Data on Humans

Feldmann and Maibach [55] studied radiolabeled hydrocortisone applied onto the skin of human volunteers, looking for radioactivity excreted in urine, and obtained important information regarding skin absorption and excretion. Contact with 0.1–0.5 ml of dimethylmercury caused the death of a scientist [56, 57]. There was an increase of mercury concentration in blood, despite the skin having been covered by latex gloves.

The use of tape stripping methods permits verification of the amount and penetration depth of metals applied on the skin of volunteers. This technique involves the standardized application of a fixed pressure during the tape stripping and permits evaluation of the penetration into the skin of nickel sulfate [22]. The same method has also been used to study nickel sulfate skin permeation using full-thickness skin under ex vivo conditions [58, 59]. The authors demonstrated that nickel was detectable in the deepest layers of the stratum corneum, the epidermis, and the dermis, with a decreasing trend. However, 42.2% of the applied dose was removed with the first two tape strips, confirming that only very small amounts of the applied metal penetrated into the viable skin. Nickel penetrating the skin can be bound by filaggrin inside the stratum corneum, as demonstrated by Ross-Hansen et al. [60].

7.7 Lag Time for Metal Penetration

In general, metals are slowly absorbed compared to solvents that can reach the steady state after less than 1 h. Experiments performed using Franz cells demonstrated a lag time of hours (Table 7.2), while experiments in vivo suggested longer periods to reach the flux steady state (70 h in [19]). A recent study demonstrated that, after the in vivo application of a patch test containing nickel sulfate 5% w/v in water in mice, maximum Ni penetration occurred after 24 h. The Ni content was high in the epidermis and spread into the dermis beyond the basal layer [61]. This experimental result confirms the penetration pattern of nickel sulfate after patch test application.

7.8 Skin Metabolism

Metals can be modified by the skin metabolism: hexavalent chromium is reduced to Cr (III) by tissue proteins, and Samitz and Katz in an old paper [62] estimated that 1 g of skin can reduce approximately 1 mg of dichromate to trivalent chromium. Arsenic accumulates in the skin, binding to proteins containing sulfhydryl groups and causing hyperpigmentation, keratoses, and skin cancer. Silver deposits inside the dermis cause a graying of the skin called argyria, and application of mercurial products causes an accumulation of metallic mercury in the skin called hydrargyrosis cutis.

7.9 Conclusion

Contact with metallic objects or with products containing metals, such as leather treated with chromium or cement containing chromium and cobalt, may result in the penetration of metals into the skin. This can cause delayed-type sensitization. The time needed for penetration in general is high, requiring hours to arrive into the dermis or pass through the skin. Sweat can increase ion release from metallic objects or substances, thereby increasing overall penetration and permeation of metals. The amount of skin permeation is generally low (ranging around ng/cm^2/h). Thus, the amount of metal that can reach the general circulation is also low and, in general, not likely to cause systemic intoxication (except for in the case of organic mercury, arsenic, and potentially lead). The presence of metals in the skin, higher in the epidermis than in the dermis, as well as the storage of metal nanoparticles inside hair follicles, can elicit local sensitization with the onset of allergic contact dermatitis. Alteration of the skin barrier, as happens in irritant dermatitis, in atopic eczema patients, and in "wet work," enhances metal penetration and permeation of the skin, increasing the risk of sensitization.

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8 Innate Immune System Response in Metal Allergy: Toll-Like Receptors

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8.1 The Significance of Innate Immune Activation in Metal Allergy

Contact allergies to normally harmless metal ions in our environment are prototypic of T cell-mediated delayed-type hypersensitivity (type IV) [1]. The capability to mount a T cell-dependent adaptive response is the key determinant governing the clinical manifestation of metal allergies. However, it is frequently neglected that *de novo* formation of metal-reactive T cells crucially requires innate immune activation [2]. In fact, the initial step in sensitization to metals is the proinflammatory activation of dendritic cells (DCs), which take up and process the metal allergen and carry it to the regional lymph node. There, they present it to naïve T cells, which become primed, proliferate and re-enter the circulation as metal-reactive effector and memory T cells (Fig. 8.1). One has to bear in mind that it is this first direct encounter between an activated DC and naïve T cells which paves the way for sensitization to metal hypersensitivity, as this interaction is a *conditio sine qua non* for *de novo* generation of metal-specific T cells. Of note, the degree of DC activation is considered to be of imminent importance for the fate of the resulting metal-responsive T cell as ineffective or partial DC activation is believed to result in generation of regulatory T cells and tolerance [3]. Thus, development of a T effector response requires robust DC activation. This may either result from direct stimulation or secondary activation due to the release of proinflammatory cytokines or damage-associated molecular patterns (DAMPs) by other skin-resident cells [4].

Besides its role during sensitization, innate immune activation is also relevant for endothelial activation at the elicitation phase of metal-induced allergic contact dermatitis. Once activated, endothelial cells induce expression of cytokines and cell adhesion receptors, which is necessary for recruitment of metal-specific effector T cells and other leukocytes from the circulation and their transmigration through the endothelial barrier to the site of challenge [5] (Fig. 8.1). The importance of endothelial activation is also evident by the observation that lack of the endothelial-specific leukocyte interaction molecule E-selectin in combination with P-selectin deficiency interfered with experimental contact hypersensitivity in mice [6]. Thus, innate immune activation is not only essential for initial production of metal-specific T cells but also crucial to recall and instruct T cell effector activity upon repeated or continuous challenge with the metal hapten.

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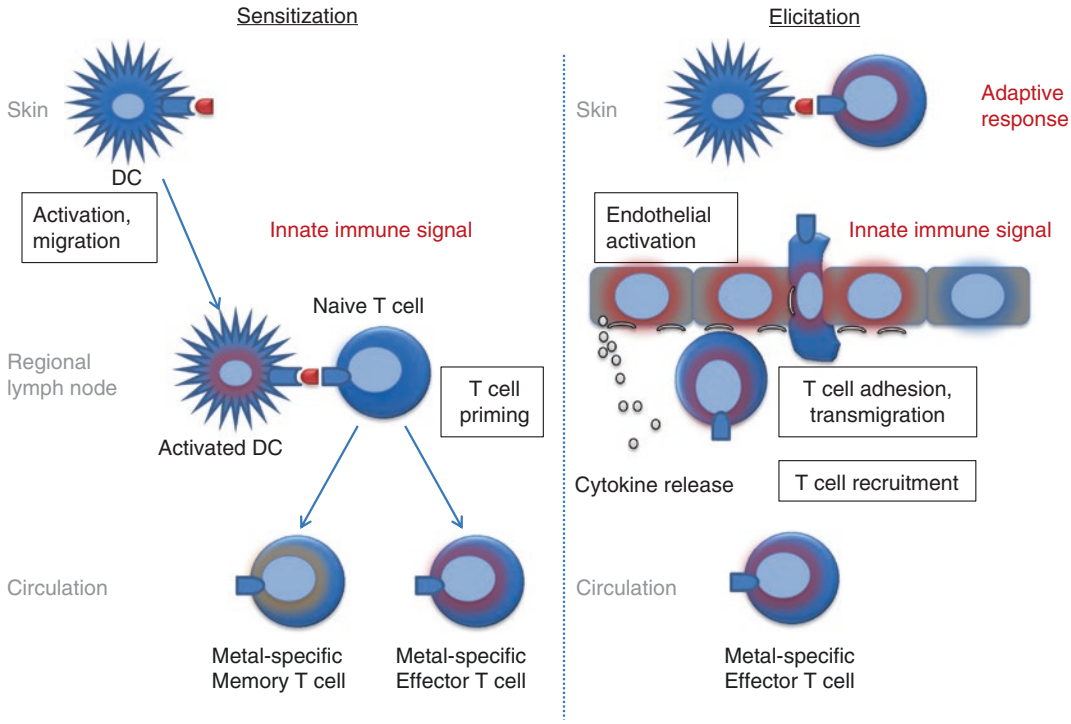

Fig. 8.1 Requirement of innate immune activation in the different phases of allergic contact dermatitis. During sensitization innate immune activation is necessary to activate and mobilize skin-resident dendritic cells, which migrate to the regional lymph node to present the metal allergen (*red*) to naïve T cells, which become primed in response to productive DC interaction. Primed metal-specific T cells subsequently proliferate and differentiate into metal-specific effector and memory T cells released to the circulation. In the elicitation phase, innate immune activation is required to locally activate endothelial cells, which in turn upregulate leucocyte adhesion receptors and cytokines to recruit metal-specific effector T cells to the site of exposure and to allow their attachment and transmigration through the endothelial barrier into the skin where they initiate the adaptive immune response by interaction with various skin-resident cells including hapten-presenting DCs

8.2 Initiation of Innate Immune Activation by Metal Allergens: The Example of Nickel

It has long been a mystery how metals initiate the required innate immune response to trigger metal allergy. For some metal allergens, the underlying mechanisms now have started to emerge. The best example is nickel, for which the mechanism of proinflammatory activation has recently been solved [7, 8].

Nickel is by far the most relevant contact allergen in humans. Still, it has never been popular as a model allergen to study contact hypersensitivity (CHS) in mice. The reason is simple: Wild-type mice are highly resistant to metal-induced contact hypersensitivity [9], making native mouse models unattractive for investigation of nickel allergy. Hence, most early studies analysing the effect of nickel on innate immunity focused on patient studies or human *in vitro* systems. Below we will briefly summarize some of the key findings that helped to shed light on the mechanism by which nickel initiates its allergic response.

An important finding was the discovery that nickel could directly trigger proinflammatory gene expression in human primary endothelial cells *in vitro* [10, 11], which later greatly facilitated identification of the responsible receptor since those cells only express a limited number of dedicated innate immune receptors. Endothelial

activation was subsequently confirmed as a physiological response to nickel exposure, as it could be demonstrated that epicutaneous nickel administration to the skin of sensitized patients resulted in strong mRNA expression of endothelial-specific inflammation markers in skin sections [12]. Intriguingly, proinflammatory activation of dermal endothelial cells as well as unidentified cells in the vicinity or within the keratinocyte basal cell layer of the epidermis was initiated as early as 6 h after nickel application [12]. At this early time point, no infiltration of T cells or other leukocytes was observed, excluding an activation mode via infiltrating leukocytes. The early activation kinetics of skin-resident cells also argued against other indirect activation mechanisms, for instance, via DAMP release that may secondarily activate innate immune receptors. This corroborated previous *in vitro* findings that stimulation of primary human endothelial cells with nickel or cobalt triggered a rapid activation of the proinflammatory IKK2/NFκB pathway and induction of NFκB-dependent gene expression [11]. Importantly, the observed inflammatory response of human primary endothelial cells did not depend on release of TNF or IL-1, which are well-known NFκB-activating cytokines since neither interfering antibodies to TNF or IL-1 [11] nor treatment with the IL-1 receptor antagonist anakinra [8] was able to block the inflammatory response to nickel. This supported the notion that nickel could directly trigger activation of an IKK2-/NFκB-inducing innate immune receptor.

8.3 Identification of TLR4 as Direct Mediator of Nickel-Induced Innate Immune Activation

Innate immune responses critically depend on activation of a relatively small number of pattern recognition receptors (PRRs) that are dedicated to the broad detection of evolutionarily conserved pathogen-associated molecular patterns (PAMPs) rather than to the detection of single pathogenic structures [13, 14]. Prominent examples are Toll-like receptors (TLRs), but PRRs additionally involve Nod-like receptors (NLRs), Rig-like receptors (RLRs) and DNA sensory proteins such as AIM2.

Among those, TLRs such as TLR2 and TLR4 qualified best as potential nickel sensors: For one, TLR2 and TLR4 had previously been shown to be important for contact hypersensitivity responses as TLR2/TLR4 double-deficient mice were resistant to contact hypersensitivity induced by the model hapten 2,4,6-trinitro-1-chlorobenzene (TNCB) [15]. Secondly, TLR4 was also shown to be involved in unrelated allergic responses such as innate immune activation by the dust mite allergen Der p2 [16] or the cat dander protein Fel D1 [17]. Finally, TLRs evolved to detect a large variety of different molecular patterns ranging from PAMPs such as bacterial lipids, glycoproteins, peptidoglycans or nucleic acids [18] to endogenous DAMPs such as hyaluronic acid [19], heat shock proteins [20], S100 proteins [21], or the extracellular matrix protein biglycan [22].

TLRs are integral glycoproteins, consisting of a cytoplasmic or luminal leucine-rich receptor domain, an anchoring transmembrane domain and an intracellular Toll-/interleukin 1-receptor (TIR) domain that mediates intracellular signal transduction in response to pathogen challenge [18]. In humans ten different functional TLRs have been described, which differ both in PAMP specificity, cellular localization and downstream signalling. They are subcategorized into cell surface TLRs, including TLR1, TLR2, TLR4, TLR5 and TLR6 due to their localization within the cytoplasmic membrane, and intracellular TLRs comprising TLR3, TLR7, TLR8 and TLR9, which reside in the membrane of endosomes, the endoplasmatic reticulum, lysosomes and endolysosomes [18]. Their different localization reflects the distinct core function of those two TLR subtypes, with surface TLRs mainly being involved in the defence of extracellular bacterial or fungal pathogens by recognition of microbial membrane components such as proteins, lipoproteins and lipids, and intracellular TLRs mediating host responses to intracellular microbes and viruses by detection of nucleic acids. Despite their fundamental differences in core functionality, the

two TLR subgroups share central downstream signalling components required for proinflammatory activation. TLR activation invariably results in activation of the IKK2/NFκB transcription factor pathway [18], which is essential for transcriptional induction of key proinflammatory cytokines such as TNF or IL-8 [23]. Except for TLR3, the capacity of TLRs to stimulate NFκB activity critically relies on recruitment of the TIR domain-containing adaptor protein, MyD88 and members of the IL-1 receptor-associated kinases (IRAKs) such as IRAK1 and IRAK4, which also are essential for mediation of signal responses downstream of the IL-1 receptor. It was particularly this critical dependency of TLR signalling on MyD88 and IRAK1 that finally implicated TLRs as mediators of nickel-induced innate immune activation since siRNA-mediated knockdown of MyD88 or IRAK1 could abrogate nickel-induced proinflammatory gene expression in primary human endothelial cells [24]. As those cells only express a limited number of TLRs including TLR4 and TLR3 [25], which triggers NFκB activation in a MyD88-independent manner via the TIR-domain-containing adapter TRIF [26], the candidate list of TLR mediators of nickel-induced NFκB activation quickly boiled down to TLR4, which physiologically detects bacterial lipopolysaccharide (LPS) [27]. Indeed, siRNA-mediated depletion of either TLR4 or its co-receptor MD2 abolished nickel-induced NFκB activity in human primary endothelial cells [24]. Conversely, reconstitution of human TLR4 along with its co-receptor MD2 but not expression of either receptor component alone or other TLRs restored the missing innate immune response of TLR-deficient HEK293 cells to nickel [24], confirming the human TLR4/MD2 complex as a nickel-responsive innate immune receptor. Surprisingly, only in human cells, TLR4/MD2 positivity turned out to be a reliable predictor of nickel-induced proinflammatory activation, whereas nickel failed to trigger proinflammatory gene expression in TLR4-/MD2-positive murine cells [24]. Consistently, expression of murine TLR4 in HEK293 cells stably expressing either murine or human MD2 was unable to restore nickel-induced proinflammatory gene expression [24]. This also explains the aforementioned insensitivity of mice to nickel-induced contact hypersensitivity since murine TLR4 was unable to initiate an innate immune signal in response to nickel stimulation. Accordingly, only transgenic expression of human TLR4 but not of murine TLR4 in a $TLR4^{-/-}$ background was capable of restoring innate immune activation by nickel and allowed for contact hypersensitivity induction by nickel in mice [24].

This peculiar species dependency of nickel-induced proinflammatory activation and contact hypersensitivity finally turned out to be due to the presence of two non-conserved histidines, i.e. H456 and H458, at the dimerization interface of human TLR4, which are missing in murine TLR4. Accordingly, mutation of the equivalent sites of murine TLR4 to histidines restored its capacity to induce nickel-dependent proinflammatory gene expression in reconstitution experiments in MD2-expressing HEK293 cells [24]. Structural modelling of dimeric human TLR4 further revealed that the non-conserved histidines at position H456 and H458 in combination with a conserved histidine at position H431 provided by the opposing TLR4 monomer form two putative metal binding sites in the assembled TLR4 dimer [24], suggesting that nickel may initiate proinflammatory signalling by cross-linking two TLR4 molecules. Indeed, this concept was validated when it was demonstrated that nickel stimulation promoted co-immunoprecipitation of differently tagged TLR4 variants co-expressed in HEK293 cells [28]. Direct interaction studies using *in vitro*-synthesized peptides comprising the predicted metal-binding region of human TLR4 later on confirmed H456 and H458 as genuine metal-binding residues [29].

Of note, the above-mentioned studies revealed important differences in nickel- and LPS-induced TLR4 activation. First, H456 and H458 were found to be dispensable for LPS-induced proinflammatory activation [24, 28]. Second, LPS required the presence of the TLR4 co-receptor MD2 to trigger TLR4 dimerization, whereas in the case of nickel, MD2 expression was not obligatory for TLR4 dimerization *per se* [28] but

strictly required for subsequent signal initiation [24], most likely by stabilizing the nickel-bound TLR4 dimer [30]. Accordingly, administration of a MD2-free soluble ectodomain of human TLR4 could reduce nickel-induced proinflammatory expression in human primary endothelial cells but left the LPS-induced response unaffected [28]. This inhibitory effect of soluble TLR4 required the dimerization capacity of the TLR4 ectodomain since neither alanine mutation of asparagine 433, which interferes with TLR4 dimerization, nor double mutation of H456/H458 of the soluble TLR4 ectodomain were able to impair nickel-induced proinflammatory activation in such transfer experiments [28]. These observations indicate that it should principally be possible to therapeutically interfere with nickel-induced proinflammatory activation without touching the innate immune system's important function in host defence against LPS-releasing gram-negative bacteria [8].

8.4 TLR-Dependent Innate Immune Activation by Other Metals

The discovery of human TLR4 as a direct mediator of nickel-induced innate immune responses raised the question whether other metal allergens might use similar mechanisms of innate immune activation. Indeed, in the meantime also other metal allergens were shown to induce proinflammatory gene expression via TLR4 or other TLRs. The first one was cobalt, which could trigger proinflammatory activation by a very similar if not identical TLR4-dependent mechanism [28, 30]. In analogy to nickel, cobalt-induced proinflammatory gene expression was similarly found to rely on human TLR4 and required MD2, TLR4 dimerization and the presence of the two non-conserved histidines H456/H458 [28, 30–33]. Analogous to nickel, cobalt further was able to trigger a type I interferon response downstream of TLR4 [30]. This most likely relied on TRIF-dependent activation of the transcription factor interferon response factor 3 (IRF3) that physiologically is initiated by endocytosis of activated TLR4, as cobalt could transcriptionally induce expression of typical TRIF-dependent cytokines such as CCL5/RANTES or CXCL10 [28] and was able to stimulate an IRF-responsive reporter construct [30].

More recently, palladium was reported as a third metal allergen to trigger TLR4-dependent proinflammatory gene expression as shown by differential responsiveness of wild-type and human TLR4-/MD2-positive HEK293 cells to palladium stimulation [34]. Consistently, other TLR4-positive cells such as primary human monocyte-derived DCs could also initiate proinflammatory gene expression in response to palladium stimulation [34]. However, the response to palladium was substantially weaker than with nickel and cobalt, and it is currently unclear whether the observed palladium response was likewise species-dependent and requiring MD2 and histidines at positions H456 and H458 of TLR4.

Apart from TLR4, TLR3 has recently not only been implicated in the elicitation phase of CHS to TNCB [35] but also the innate immune response to gold particles used in dental applications. It was demonstrated that gold thiosulphate dose-dependently triggered proinflammatory activation in TLR3-positive primary human monocyte-derived DCs and TLR3-supplemented HEK293 cells [36]. The exact mechanism of TLR3 activation, however, is currently unclear. Considering that TLR3 belongs to the group of intracellular TLRs and has been shown to serve as an endogenous sensor for RNA species formed during necrosis [37], it is conceivable that DAMP release in response to cellular damage triggers this response. Alternatively, phagocytosed gold particles may trigger nonphysiological signalling by directly influencing TLR3 activity independently of its natural ligand.

8.5 Indirect Roles of TLRs in Metal Allergy

Besides their role as direct mediators of metal-induced proinflammatory signalling (Fig. 8.2a), TLRs may exert important indirect roles in metal-

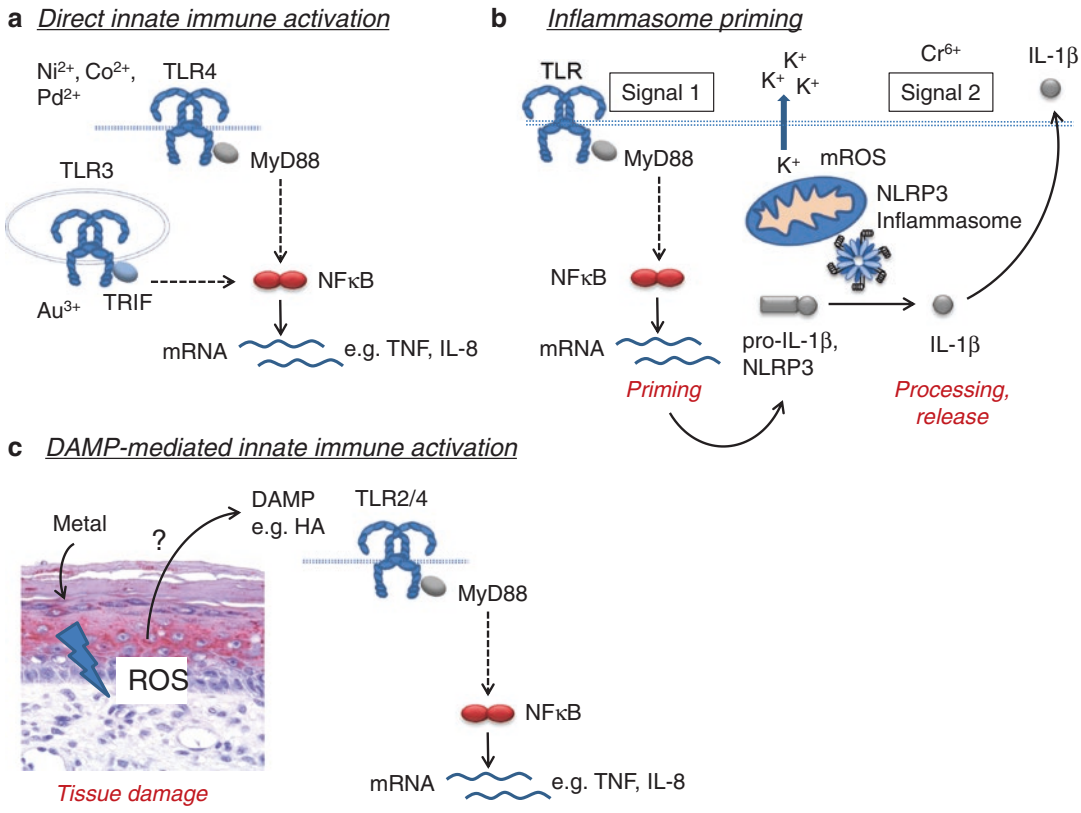

Fig. 8.2 Roles of TLRs in metal-induced innate immune activation. TLRs can either directly mediate metal-induced innate immune activation as in case of TLR4 activation by nickel (Ni^{2+}), cobalt (Co^{2+}) and Pd^{2+} or TLR3 stimulation in response to exposure with gold (Au^{3+}) particles, resulting in NFκB-dependent proinflammatory gene expression (**a**), or indirectly contribute to metal-induced innate immune responses, e.g. by priming of inflammasome activation as shown for hexavalent chromium (Cr^{6+}) (**b**) or by triggering proinflammatory gene expression in response to hypothetical DAMP release by tissue damage, for instance, by oxidative degradation of extracellular matrix components due to metal-induced production of reactive oxygen species (ROS) (**c**). *HA* hyaluronic acid, *mROS* mitochondrial reactive oxygen species

induced innate immune activation (Fig. 8.2b, c). For instance, TLR activation critically contributes to inflammasome activation [38] (Fig. 8.2b), another important innate immune mechanism known to contribute to contact hypersensitivity [39]. The inflammasome, in its core composed of a NLR (in most cases NLRP3), the adaptor protein ASC and Caspase-1, regulates maturation of IL-1β and IL-18 via Caspase-1-mediated proteolytic cleavage [38]. Importantly, inflammasome activation commonly requires a TLR-dependent priming signal that triggers pro-IL-1β and pro-IL-18 mRNA expression (signal 1) before Caspase-1-mediated release can be initiated by a distinct NLR-inducing signal (signal 2) [38] (Fig. 8.2b). Additionally, TLR-mediated priming was also found to be essential for transcriptional and post-transcriptional activation of NLRP3 [40, 41], without which no effective inflammasome activation can occur. Thus, TLR activation is considered an important prerequisite for inflammasome activation.

An intriguing example illustrating the importance of TLR signalling for metal-induced inflammasome activation is the innate immune response to chromium (Fig. 8.2b). Recent studies from our lab have shown that the major allergenic oxidation form of chromium, chromium (VI), unlike nickel or cobalt, fails to trigger pro-inflammatory gene expression in various cells

including THP-1 cells [42], a human monocytic cell line expressing multiple TLRs including TLR4 [43] that frequently is employed as a model system for studying inflammasome activation. This suggested that chromium (VI) is unable to trigger a direct TLR4-dependent innate immune signal, confirming previous observations that chromium (VI) failed to trigger innate immune activation in TLR4-positive human primary endothelial cells [11]. However, when THP1 were primed by TLR stimulation, they strongly initiated IL-1β cleavage, Caspase-1 activation and IL-1β release, indicative of inflammasome activation [42]. Knockdown of NLRP3 abolished this response, identifying NLRP3 as the responsible NLR for inflammasome activation. Chromium (VI)-induced inflammasome activation subsequently was also shown to occur in other cells, including murine bone marrow-derived DCs and human primary keratinocytes. Remarkably, the latter cells still required priming by TNF or TLR stimulation to trigger a significant inflammasome response to chromium (VI) albeit they constitutively express pro-IL-1β [42], suggesting that even in cells with basal pro-IL-1β expression, TLR-mediated priming is important to allow chromium (VI)-induced innate immune activation. Of note, only hexavalent chromium, but not trivalent chromium that is substantially less allergenic [44–46], was able to trigger NLRP3 activation [42]. While evidence is still pending to prove that inflammasome activation indeed contributes to chromium (VI)-induced contact hypersensitivity and may account for the divergent allergenicity of the different chromium compounds, these data strongly suggest that some metal allergens may critically rely on additional signals such as TLR activation present at sensitization to trigger sufficient innate immune activation to launch an adaptive immune response.

While in the case of chromium (VI), TLR activation and inflammasome activation cooperate to trigger sufficient innate immune activation, experimental data in mice also suggest that TLR stimulation can fully replace a missing innate immune signal. For instance, it has been shown that naturally nickel-resistant mice can be sensitized to nickel by co-treatment with the TLR4 agonist LPS [9] or the TLR2 agonist Pam3CSK4 [47]. This suggests that in the presence of sufficient TLR activation, for instance, by a coincidental infection, even metals normally incapable of initiating an innate immune response by themselves may efficiently trigger an adaptive response as long as they are efficiently haptenized. It is further conceivable that even in the case of metals that efficiently can activate the innate immune system such as nickel, a supporting unrelated TLR activation may be required for efficient sensitization as local nickel concentrations in the skin might not reach sufficient levels for effective TLR4 activation. On the other hand, a strong TLR4 activator such as nickel may act as an adjuvant for sensitization to another metal hapten, e.g. to cobalt [48].

Another yet unproven possibility by which TLRs indirectly may foster metal allergy is their secondary activation by DAMPs (Fig. 8.2c) [49]. For instance, it has been shown that some DAMPs produced via oxidative degradation of the extracellular matrix such as low molecular weight hyaluronic acid can act as ligands for TLR2 and TLR4 [19]. Notably, several metals including nickel and chromium (VI) trigger the release of ROS in the mitochondria [42, 50] so that *in vivo* a secondary TLR2/TLR4 activation via DAMPs produced after oxidative degradation of the extracellular matrix is at least conceivable. DAMP-mediated inflammasome activation that occurs independently of TLR4-mediated innate immune activation has recently been reported in cobalt-induced implant-related inflammation [51]. Such mechanisms may perhaps also explain why some groups, in contrast to our own experience, were able to induce contact hypersensitivity to nickel in mice, even in TLR4-deficent animals, when high doses of nickel were epicutaneously and repeatedly applied to the skin [52]. In combination with its known capacity to trigger species-independent inflammasome activation [50], this may result in sufficient innate immune activation to allow for adjuvant-free induction of contact hypersensitivity in this particular model.

8.6 Conclusion

Successful initiation of contact allergy to metals requires an antigen stimulus leading to an adaptive immune response, as well as a proinflammatory danger signal. Potent metal allergens are able to generate both at the same time. The innate signal is delivered by activation of TLRs and/or the inflammasome. Metal allergens may directly (e.g. nickel and cobalt, which directly bind to distinct histidines of TLR4 resulting in receptor dimerization and activation) or indirectly (e.g. by damaging extracellular matrix molecules such as hyaluronan that serve as TLR ligands) activate TLRs resulting in DC maturation and activation as well as expression of proinflammatory cytokines, chemokines and adhesion molecules. Moreover, as exemplified by dichromate, they may activate the inflammasome via mitochondrial ROS production, which leads to release of IL-1β and IL-18. Importantly, TLR activation may prime the inflammasome, making the latter susceptible for subsequent activation by distinct metal allergens. Finally, the coincident presence of microbial pathogens can contribute to (or even supplement for) the delivery of the required metal allergen innate immune signal. A deeper understanding of the sensing of metal allergens by the innate immune system will surely contribute to the development of novel therapeutic approaches for this common allergic skin disease.

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9 Acquired Immunity in Metal Allergy: T Cell Responses

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9.1 Introduction

Metal ions are common triggers of allergic contact dermatitis (ACD) [1]. ACD is a T cell-mediated inflammatory response classified as a type IV delayed-type hypersensitivity reaction. ACD can be divided into two phases—the sensitization and the elicitation phase (Fig. 9.1) [2]. Sensitization occurs after contact with a specific allergen and requires activation of the innate immune system in the skin, eventually leading to the activation and migration of dendritic cells (DC) to the draining lymph nodes [3]. In the lymph nodes, the DC presents the allergen in association with a major histocompatibility complex (MHC)-bound peptide to naïve T cells expressing an allergen-specific T cell receptor (TCR) [4]. These events lead to clonal expansion of the allergen-specific T cells and generation of allergen-specific memory T cells that can be found in both skin and blood. During re-exposure to the specific allergen in the elicitation phase, allergen-specific memory T cells are recruited and activated, resulting in the cellular damage and inflammation responsible for the clinically apparent eczematous skin reaction [2]. In this chapter, we focus on T cell responses to metals with special emphasis on the response to nickel, as nickel allergy is the most common and thoroughly studied of the metal allergies.

9.2 Presentation and T Cell Recognition of Metal Ions

T cells recognize antigens in the form of MHC-peptide complexes via their TCR. The TCR is composed of the variable, antigen-recognizing TCRα and β chains in the majority of circulating T cells and the TCRγ and δ chain in a minority of circulating T cells. Together with the invariable chains CD3γ, CD3δ, CD3ε, and ζ, which are responsible for signaling, the antigen-recognizing chains make up the complete multimeric TCR (Fig. 9.2a). To be recognized by the TCR, an antigen must be processed into peptides and presented on MHC molecules. Two major classes of MHC molecules present peptides to the TCR, namely, MHC class I and MHC class II molecules. $CD8^+$ and $CD4^+$ T cells recognize MHC class I-peptide and MHC class II-peptide complexes, respectively (Fig. 9.2b). Like most other contact allergens, metal ions are low molecular weight chemicals (< 500 Da) referred to as haptens, which have to bind proteins or peptides to become immunogenic. Most of our knowledge about the way nickel is presented to T cells comes from studies using isolated nickel-reactive T cell clones from patients

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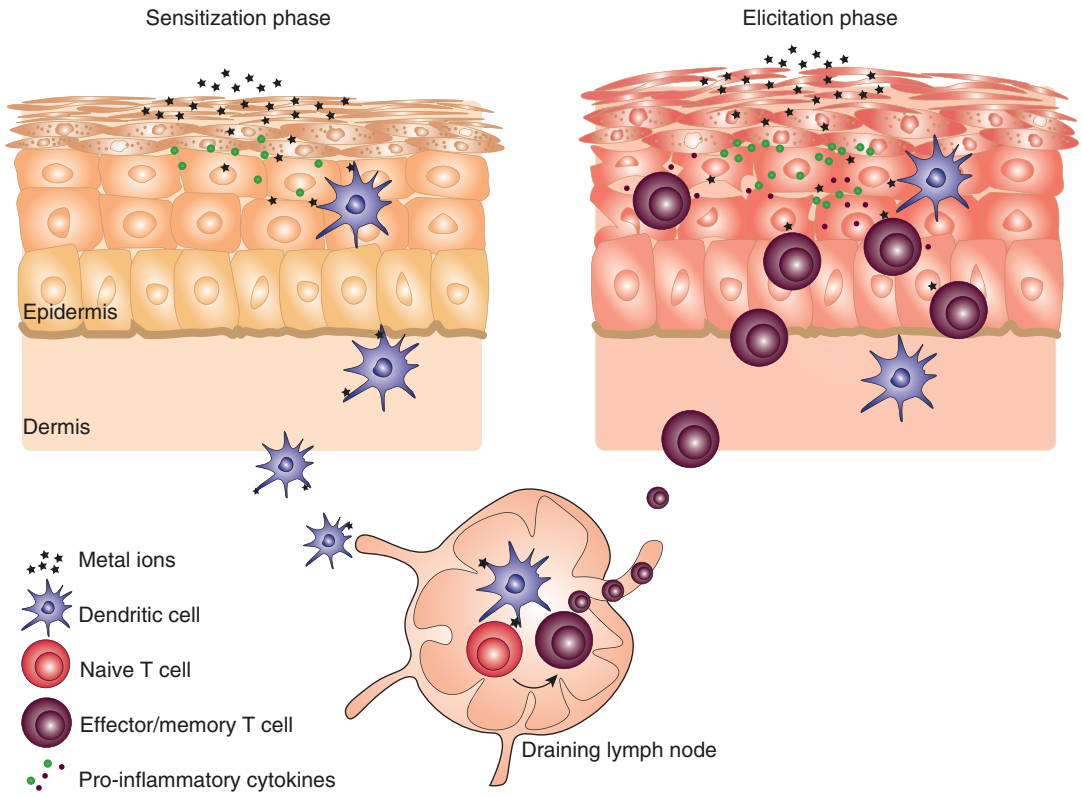

Fig. 9.1 The immunological mechanisms of contact allergy. In the sensitization phase, allergens (e.g., metal ions) penetrate the skin and trigger activation of an innate inflammatory response with the production of pro-inflammatory cytokines, eventually leading to activation of dendritic cells (Langerhans cells in the epidermis and dermal dendritic cells in the dermis). The DC migrate to the draining lymph nodes and present the allergen to naïve allergen-specific T cells, which leads to clonal expansion and generation of allergen-specific memory T cells. Upon re-exposure to the same allergen in the elicitation phase, memory T cells are recruited and activated, mediating skin inflammation and cellular damage

with nickel allergy [5]. Stimulation of these clones with nickel ions (Ni^{2+}) could induce strong proliferative responses, showing that T cells are involved in the pathogenesis of nickel allergy [6–9].

Metal ions are proposed to be presented to T cells much like classical haptens by forming complexes with amino acid residues on the MHC molecules and/or on the MHC-bound peptides [10] (Fig. 9.3a). However, unlike classical haptens, metal ions do not form stable covalent bonds to proteins. They rather interact with nitrogen or oxygen in amino acid side chains to produce non-covalent, reversible coordination protein-metal complexes [2, 5]. The first study indicating that nickel could bind an MHC-bound peptide was published in 1991. In this study, it was found that T cell clones reactive to a malarial peptide were inhibited from recognizing the peptide by treatment of the peptide-pulsed, antigen-presenting cells (APC) with Ni^{2+} [11]. A histidine (His) residue of the malaria peptide was found to be responsible for the binding of Ni^{2+}. Similar findings were later reported for gold [12, 13].

In 2003, Lu et al. studied the components of the ligand for a human nickel-reactive $CD4^+$ T cell clone (ANi-2.3) that had been isolated from a patient with nickel allergy [14]. ANi-2.3 belongs to a group of TCR-Vβ17-expressing T cells that are found to be overrepresented among nickel-specific $CD4^+$ T cells in patients suffering from particularly severe nickel allergy [15, 16]. Lu et al. identified the MHC restriction element

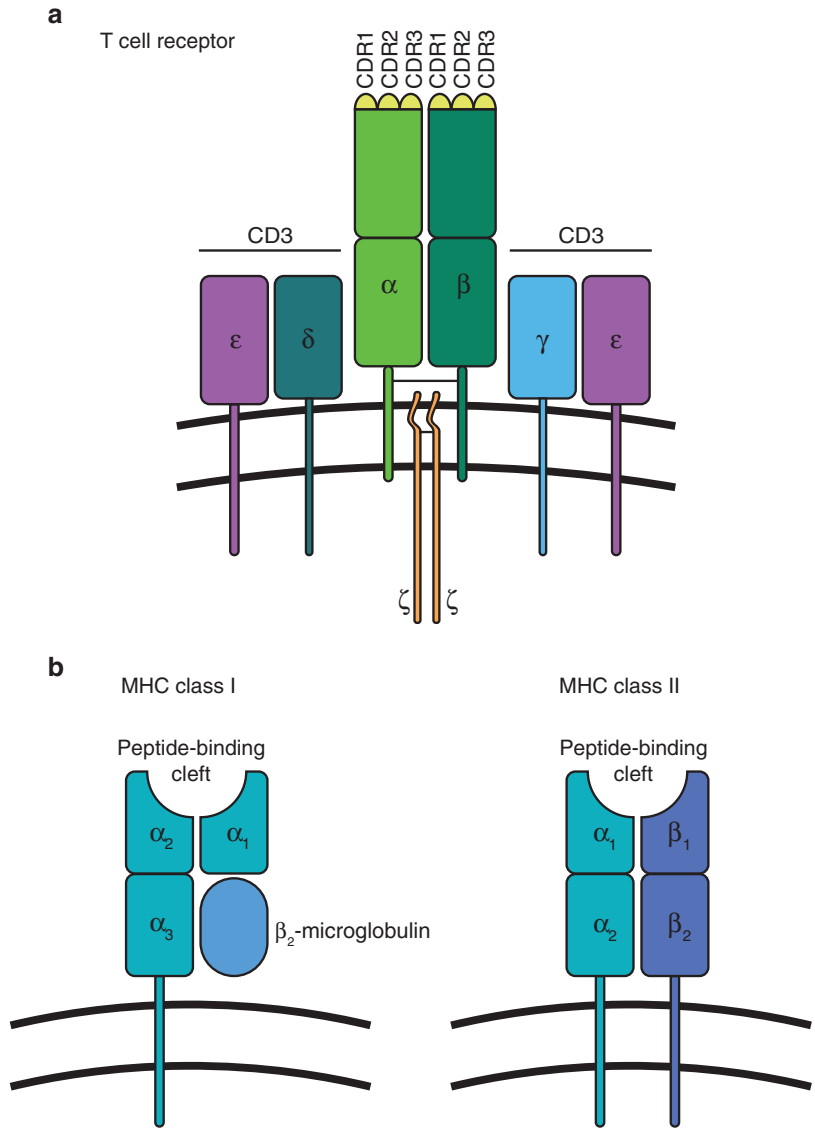

Fig. 9.2 Composition of (**a**) the T cell receptor (TCR) and (**b**) major histocompatibility complex (MHC) classes I and II

for ANi-2.3 as HLA-DR52c [14]. They found that the functional ligand for this T cell clone was a complex of Ni^{2+} bound to the combination of HLA-DR52c and an unknown peptide produced in B cells. Furthermore, Ni^{2+} could be presented to ANi-2.3 by paraformaldehyde-fixed autologous APC, which indicated that Ni^{2+} can be presented on preformed MHC-peptide complexes [14]. In addition, it was shown that ANi-2.3 recognition of the Ni^{2+}-MHC-peptide complex was dependent on His81 of the HLA-DR52c β chain—a residue that is conserved in the β chain of many MHC class II molecules. It was proposed that Ni^{2+} was coordinated by His81 and by two amino acid side chains of the bound peptide. As ANi-2.3 is cross-reactive to copper and gold cations, it was speculated that these could be coordinated similarly to Ni^{2+} [14]. Unfortunately, a crystal structure of the complete complex of TCR, MHC class II, peptide, and Ni^{2+} does not exist [17]. However, recently a screening of libraries of DR52c-bound peptides with ANi-2.3 resulted in the identification of so-called mimotope peptides that could substitute for Ni^{2+} and

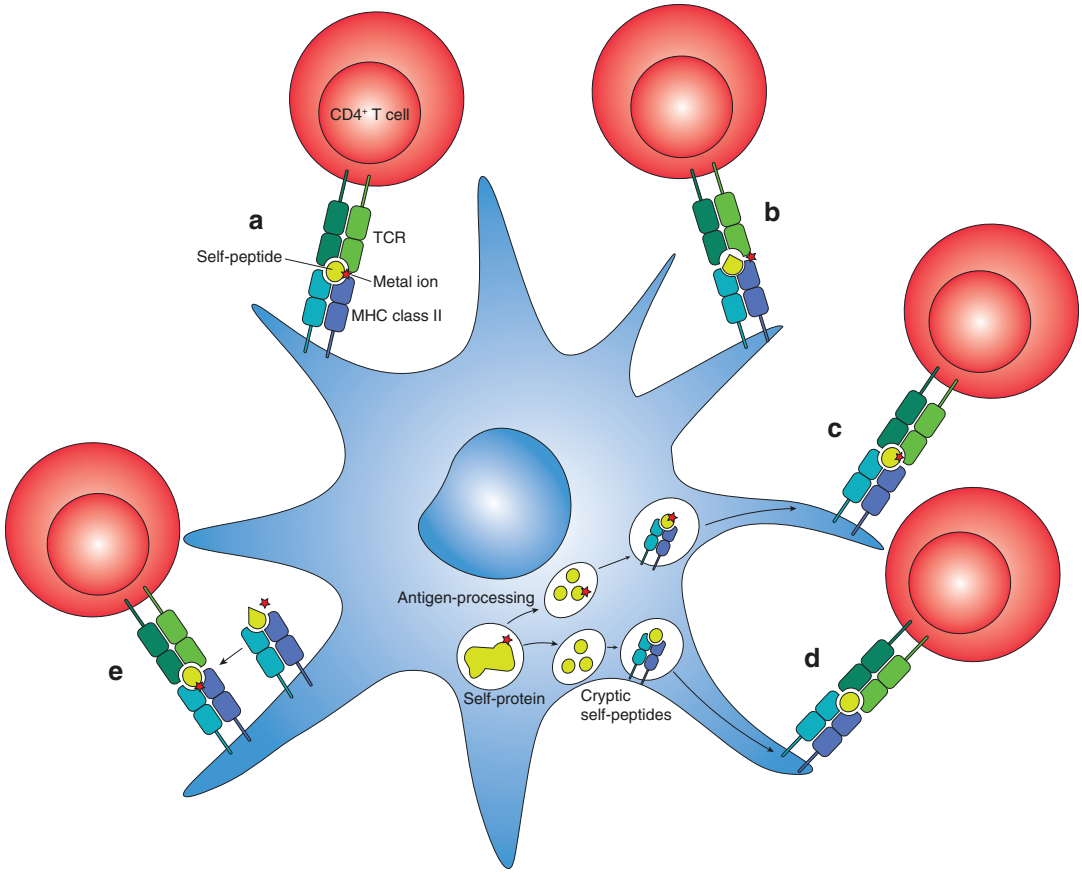

Fig. 9.3 Models of metal presentation to CD4⁺ T cells. Several different molecular interactions between metal ions, the TCR, and MHC class II-peptide complexes have been proposed. (**a**) Metal ions can directly bind to the MHC molecule and the associated peptide, or it can bind to either the peptide or the MHC molecule only (not shown). (**b**) Similarly to superantigens, metal ions might directly bridge TCR with MHC, independent of the MHC-associated peptide. (**c**) Some MHC-peptide-metal complexes may be formed by cellular processing of metal-modified proteins, and (**d**) in other instances, metal ions may alter the processing of self-proteins and trigger activation of T cells with metal-free cryptic self-peptides. (**e**) Some metal ions may create neo-antigens by altering the conformation of preexisting self-MHC-peptide complexes. The TCR subsequently recognizes the neo-antigen but does not directly interact with the metal ion

the self-peptide in the natural TCR ligand [18]. By solving the structure of two of these mimotopes, insight was offered into the binding site for Ni^{2+} in the natural ligand and how it interacts with the TCR [18]. Thus, structural analyses revealed that ANi-2.3 TCR docked on the mimotope peptide-DR52c complex in a typical diagonal orientation, and it was suggested that a conserved lysine residue at the p7 position of the DR52c-bound peptide mimicked Ni^{2+} in the natural TCR ligand [18]. Supporting that the ANi-2.3 TCR interacts with Ni^{2+} complexed to a self-peptide, this study further showed that Ni^{2+} and maybe also other metal cations were accommodated by an acidic pocket formed by the α1 and β1 chains of DR52c in the peripheral region of the peptide-binding groove where the conserved p7 lysine of the peptide mimotope was located [18, 19]. Future structural studies similar to this might provide a more complete understanding of metal recognition by T cells [17].

Gamerdinger et al., who studied another CD4⁺, TCR-Vβ17-expressing nickel-reactive T cell clone (SE9), identified a second and quite

different type of Ni^{2+} recognition. As shown for ANi-2.3, nickel reactivity of SE9 did not depend on antigen processing as it could be activated in the presence of fixed APC, but in this case Ni^{2+} recognition was also found to be independent of the nature of the MHC-associated peptides. On the other hand, SE9 cells required permanent availability of Ni^{2+} in the medium for activation, arguing against the existence of preformed Ni^{2+}-MHC determinants for the SE9 TCR [20]. Furthermore, SE9 activation crucially depended on the conserved His81 in the HLA-DR β chain, as well as on two tyrosine residues in the CDR1 and CDR3 region of the TCRα chain (Fig. 9.2a). Thus, it was proposed that Ni^{2+}, in analogy to superantigens, directly links and stabilizes intramolecular bridges between the TCR and MHC independently of MHC-associated peptides [20] (Fig. 9.3b). Whether this proposed model also applies to other metals remains unknown, as the SE9 clone was not cross-reactive to copper, palladium, cobalt or chromium [20]. In addition, it has been suggested that particular proteins such as human serum albumin could be responsible for transferring Ni^{2+} to the high-affinity coordination sites within the contact zone between certain TCR and MHC molecules [5, 21].

Activation of ANi-2.3 and SE9 by Ni^{2+} was not dependent on active antigen processing. However, this does not account for all isolated nickel-reactive clones. A study on 42 independent T cell clones showed that 40% of the clones could not be activated by glutaraldehyde-fixed APC, meaning that these were strictly dependent on active antigen processing [8]. Thus some MHC-peptide-metal complexes may be formed by cellular processing of metal-modified proteins [9, 10] (Fig. 9.3c). In this context, it has been suggested that metal ions in some instances alter the processing of self-proteins and trigger activation of T cells with metal-free cryptic self-peptides [22, 23] (Fig. 9.3d). Moreover, it has been shown that certain noble metals, including palladium and gold, are able to destabilize peptide binding to MHC class II complexes, whereby the metal-bound MHC molecule adopts a stable, "peptide-empty" conformation that resembles the transition state of peptide loading [24]. This metal-induced peptide stripping may also be involved in the formation of new antigenic epitopes. Hence, although not tested in the study, the peptide-empty MHC molecules could be recognized by certain T cells as neo-antigens [17, 24]. Some metal ions may also create neo-antigens by indirect modification of preexisting self-MHC-peptide complexes as shown for beryllium ions (Be^{2+}) in a study on chronic beryllium disease [25]. Here, it was shown that the TCR did not interact directly with Be^{2+}. Instead, Be^{2+} was buried in an MHC-peptide complex, altering the charge and conformation of the surface of the complex, which was then recognized by the TCR [25] (Fig. 9.3e).

The studies described above reveal that several different molecular interactions between metal ions, the TCR and MHC class II-peptide complexes must be considered in $CD4^+$ T cell responses to metals (Fig. 9.3). How nickel and other metals are presented to $CD8^+$ cells by MHC class I molecules is still not known, but similar mechanisms as described for $CD4^+$ T cells probably apply. It is known that the strength whereby a TCR is triggered affects the resulting effector T cell response [26]. How metals are presented to T cells therefore most likely has a great impact on the T cell response and thereby the development of ACD. Specifically, modulation of metal presentation could potentially be useful for the development of more specific treatments of metal allergies.

9.3 $CD4^+$ Versus $CD8^+$ T Cells in Metal Allergy

T cells involved in metal allergy seem to be a very heterogeneous group with regard to their cytokine profile and function. Early studies on blood-derived nickel-specific T cell clones suggested that nickel allergy was a $CD4^+$ Th1-dominated response mainly mediated by IFN-γ [6, 27]. The important role of $CD4^+$ cells in the response have been confirmed by several studies showing the involvement of both Th1 and Th2 components in nickel allergy [28–31] as well as in allergies to other metals, including palladium,

cobalt, chromium, and gold [32, 33]. However, Cavani et al. compared the characteristics of the T cell responses to nickel in allergic patients and healthy individuals [34]. They found that both allergic and nonallergic individuals carried $CD4^+$ memory T cells responsive to nickel. In contrast, they found that nickel-specific $CD8^+$ T cell responses were restricted to the nickel-allergic patients. Nickel-specific $CD8^+$ T cell clones expressed the skin-homing marker cutaneous lymphocyte-associated antigen (CLA) and released high amounts of IFN-γ and no IL-4, thus belonging to the T cytotoxic 1 (Tc1) subset [34]. In contrast, both allergic and nonallergic individuals carried $CD4^+$ memory T cells responsive to nickel. The nickel-specific $CD4^+CLA^+$ T cell clones from the nonallergic donors secreted higher amounts of IL-10 and lower amounts of IFN-γ compared to the T cell clones from the allergic patients. From these results, it was concluded that $CD8^+$ T cells are crucial for the induction of nickel allergy, whereas $CD4^+$ T cells may predominantly have a regulatory role [34]. In the same year, another study also demonstrated the presence of nickel-specific $CD8^+CLA^+$ T cells in the peripheral blood of nickel-allergic individuals [35]. Although the $CD8^+$ T cells only constituted a minor subpopulation of the nickel-specific T cells, which had also been shown by others [28], they clearly had effector functions in the presence of nickel, involving cytokine production (IFN-γ and some IL-4 in addition) and cytotoxic activity [35]. Traidl et al. further demonstrated an important role of $CD8^+$ T cells in nickel allergy, as nickel-loaded keratinocytes were found to be highly susceptible to nickel-specific cytotoxicity induced by skin-infiltrating $CD8^+$ Tc1 and Tc2 cells [36].

However, the role of $CD8^+$ cells has been questioned [37]. By using T cells isolated directly from peripheral blood mononuclear cells (PBMC), Moed et al. showed that only $CD4^+CLA^+CD45RO^+$ and not $CD8^+$ T cells proliferate and produce both Th1- (IFN-γ) and Th2-type (IL-5) cytokines in response to nickel [37]. In line with this, Minang et al. examined the role of $CD4^+$ and $CD8^+$ T cells on nickel-induced Th1- and Th2-type cytokine production. By depleting $CD4^+$, $CD3^+$, or $CD8^+$ T cell populations from PBMC, they showed that $CD4^+$ T cells were responsible for the nickel-specific production of both IFN-γ and IL-4 [38]. Thus, these studies suggested that $CD4^+$ T cells are the most important effector cells in nickel allergy. In accordance, we have demonstrated a massive cellular infiltration in nickel-challenged skin from nickel-allergic patients with $CD4^+$ T cells being the predominant cells [39]. However, $CD8^+$ T cells were also found in the infiltrate [39], suggesting that at least small numbers of $CD8^+$ nickel-specific T cells contribute to nickel-induced allergic skin reactions.

The varying results presented above might be ascribed to the use of different experimental models, e.g., the use of long-term cultured T cell clones or freshly isolated T cells from blood or skin, as well as patient-related differences [37]. Thus, although there is some inconsistency concerning the roles of $CD4^+$ versus $CD8^+$ T cells during the response to nickel, we find it likely that both subsets play important roles as effector cells probably in different phases of the response. Accordingly, we have recently shown that exposure to nickel in nickel-allergic individuals results in localization of epidermal-resident memory $CD8^+$ T cells in the specific skin area exposed to nickel [40]. Even though the epidermal-resident memory $CD8^+$ T cells appear to be a minor subset during the peak of the ACD response, they probably boost the innate immune response and thereby are important initiators and accelerators of the early inflammatory response [39, 40].

9.4 Th17 Cells and Nickel Allergy

Although the studies described above point toward metal allergy being a Th1/Tc1-dominated or a mixed Th1/Th2 response, evidence for the involvement of other T cell subsets has emerged. Thus, Albanesi et al. found that IL-17 mRNA was expressed in skin biopsies from positive patch tests to nickel but not in normal skin [41]. In addition, IL-17 was found to be produced by approximately 50% of activated blood- and skin-derived nickel-specific $CD4^+$ T cell clones,

although the authors did not find IL-17 production to segregate into a distinct Th subset [42]. Rather, IL-17 was produced together with either IFN-γ (Th1), IL-4 (Th2), or both (Th0), and it was demonstrated that IL-17 modulated various pro-inflammatory functions of keratinocytes, especially when acting together with IFN-γ and IL-4 [41, 42]. We have identified nickel-specific Th1 and Th17 cells in the circulating memory T cell compartment from nickel-allergic patients but not from healthy controls following restimulation with autologous nickel-pulsed DC [43]. Furthermore, we showed infiltration of cells expressing IL-17, IL-22, CCR6, as well as the IL-22 receptor in an inflamed skin of nickel-challenged allergic individuals [43]. These findings have been confirmed by a study showing that IL-17-producing $CD4^+$ T cells infiltrate the skin during ACD elicited by nickel, cobalt, fragrances, or thiuram [44]. One way IL-17 seems to amplify the allergic skin reaction is by acting synergistically with IFN-γ to increase T cell-keratinocyte adhesiveness via ICAM-1, which promotes the Fas-FasL-mediated T cell killing of keratinocytes [44]. In addition to IFN-γ and IL-17, IL-22 seems to be involved in the response as increased serum levels of IL-22 have been found in nickel-allergic individuals [45]. In correlation with this, we have shown that the number of IL-17-, IFN-γ-, and IL-22-producing $CD4^+$ T cells is increased in skin-derived T cell pools from nickel-exposed skin compared to vehicle-exposed skin from nickel-allergic patients [39]. Thus, these studies suggest that Th17 and Th22 cells are also important effector cells in nickel allergy and presumably in other metal allergies as well. Accordingly, IL-17 and IL-22 stimulate keratinocytes to release IL-1β, a cytokine that is indeed associated with ACD and nickel allergy [46–48]. Furthermore, IL-1β may provide positive feedback for further IL-17 and IL-22 production [49, 50].

The involvement of Th17 and Th22 cells in metal allergy was recently substantiated by Dhingra et al. who performed extensive molecular and cellular profiling of skin samples from patients sensitized to several common haptens, including nickel and other metal allergens, compared to petrolatum-occluded skin. Using RT-PCR, gene arrays, and immunohistochemistry, nickel was found to induce potent innate immune responses and Th1/Th17 polarization along with a Th22 component. Other metals, including cobalt and chromium, generally showed weaker immune activation predominantly characterized by induction of Th17 markers [51].

9.5 Induction of Regulatory T Cells in Nickel Allergy

As mentioned above, nickel allergy is the most frequent form of ACD, affecting approximately 14.5% of the general European population [52]. However, as nickel is ubiquitously present in our everyday life, one would expect that even more people developed nickel allergy or that different types of immune responses (pro- or anti-inflammatory) could develop depending on the route and dose of the primary nickel exposure. The development of nickel tolerance was suggested based on epidemiological studies and was later confirmed in both human studies and in animal models [34, 53–58]. Interestingly, it was shown that oral contact with nickel in the form of dental braces prior to ear piercing reduced the risk of developing nickel allergy by approximately 50% [53]. Later, it was shown that oral tolerance correlated with the induction of nickel-specific IL-10 production by PBMC [30]. The mechanisms for oral tolerance to metal have been further studied using different animal models. It was shown that it is possible to induce long-lasting (> 2 years) nickel-specific tolerance in a dose-dependent manner by feeding guinea pigs $NiSO_4$ [55]. Similar results were obtained by feeding animals with chromium [55]. The mechanism mediating this tolerance seems to be the induction of suppressor cells as the tolerance could be transferred to naïve animals by transferring spleen and lymph node cells from nickel-fed animals [55]. Studies in mice confirmed the induction of oral tolerance by giving mice $NiSO_4$ in the drinking water, and it was shown that the cells mediating the suppression were $CD8^+$ T

cells [56, 57]. In contrast, in a series of studies, Gleichmann and co-workers showed that both CD4⁺ and CD8⁺ T cells are required to obtain oral tolerance to nickel and that the T cells work together with both tolerogenic APC and CD4⁺ invariant NKT cells [58–62]. The different results obtained in various studies might be due to the use of different mice strains and/or doses of nickel [56–58]. Interestingly, when comparing the effector function of nickel-responsive T cell clones isolated from nickel-allergic and healthy controls, it was shown that in healthy controls only CD4⁺ T cells proliferated following nickel stimulation, whereas the proliferation of both CD4⁺ T cells and CD8⁺ T cells was seen in allergic individuals [34]. The CD4⁺ T cell clones isolated from healthy controls were characterized by high production of IL-10 compared to the CD4⁺ T cell clones isolated from nickel-allergic individuals [34]. The nickel-specific IL-10-producing CD4⁺ T cells (Tr1 cells) were further analyzed and they were identified both in blood and skin from nickel-allergic individuals and in blood from healthy controls [63]. The nickel-specific Tr1 cells were shown to inhibit the maturation of dendritic cells and monocytes via an IL-10-dependent mechanism, thereby inhibiting the activation of Th1 and Tc1 cells [63]. The presence of anti-inflammatory mechanisms in individuals with negative patch tests was confirmed by Rustemeyer et al., who found a higher number of individuals with blood-derived, nickel-specific IL-10- and TGF-β-producing T cells among a group of individuals with negative patch tests compared to a positive patch test group [30]. In addition to Tr1 cells, CD4⁺CD25⁺ T cells (Treg cells) with an anti-inflammatory function have been isolated from nickel-patch test negative skin [54]. Interestingly, Treg cells could inhibit both primary and secondary nickel-specific responses in a cell-cell contact-dependent and IL-10- and TGF-β-independent way [54]. The induction of tolerance in already allergic individuals has been studied using a mouse model for oral nickel desensitization [58]. Unfortunately, even though it was possible to desensitize allergic mice, this required constitutive oral exposure to nickel [58].

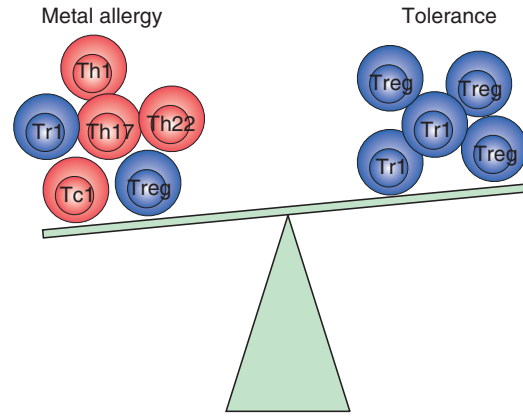

Fig. 9.4 T cells involved in metal allergy. Metal allergy is a T cell-mediated reaction with Tc1, Th1, and Th17 cells being the major effector cells and Tr1 and Treg cells having an anti-inflammatory role

9.6 Conclusion

T cells play a central role in immune responses to metals, with Tc1, Th1, and Th17 cells being the major effector cells and Tr1 and Treg cells having an anti-inflammatory role (Fig. 9.4). However, additional studies are clearly required to define the exact role of the different T cell subsets in metal allergy. For example, it has been suggested that Th2 responses to metals and other contact allergens are elicited to counterbalance the detrimental Th1/Tc1 responses [1, 38, 64]. In addition, a study recently found that nickel increases IL-9 production in human PBMC from nickel-allergic patients but not from healthy donors. It was suggested that Th9 cells exert a regulatory role in nickel allergy by modulating the Th1 response both directly and via its ability to promote secretion of the Th2 cytokine IL-4 [65]. Finally, it would be highly valuable to understand the immunological mechanisms underlying the fact that only temporary desensitization can be induced in individuals with metal allergy.

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Metal Allergy and Tolerance Development

10

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10.1 Introduction

Metals are widely distributed in our environment: they are present in the Earth's crust, usually as oxides, sulphides and silicates, and only the precious metals are in metallic form. Metallic compounds occur naturally in drinking water and food, and some elements are essential nutrients in all forms of life. Nowadays, these substances are used with high frequency worldwide, such as in industrial processes and consumer products (jewellery, cosmetics, paints, leather, dental materials, household products, dyes, personal adornments, pharmaceuticals, etc.).

The ubiquity of these elements and the industrialization of the last century led to growing cutaneous exposure and, consequently, rising incidence of occupational and health hazards. Some of these metals are well-known potent contact allergens capable of inducing allergic contact dermatitis (ACD), a delayed-type hypersensitivity (DTH) response, in susceptible individuals upon prolonged direct exposure [1]. ACD is a disease with economic and psychological impact on society. It has been estimated that around 10–15% of the adult population in many parts of the world is sensitized to one or more metal contact allergens [2, 3].

A recent analysis by the European Surveillance System on Contact Allergy network (ESSCA; www.essca-dc.org), based on 2002–2010 patch test data across Europe, shows a high frequency of sensitization to nickel (Ni), cobalt (Co) and chromium (Cr) with prevalence rates of around 23.4%, 9.3% and 5.6%, respectively [4]. Similarly, the North American Contact Dermatitis Group (NACDG) reported positive responses to Ni in 19.5%, Co in 8.4% and Cr in 4.1% of the 5085 patch-tested subjects [5].

Ni- and Co-induced ACD is considerably more common in women than men. This gender difference is traditionally explained by increased exposure in women to direct skin contact with metal release, such as via piercings and jewellery. On the other hand, Cr ACD affects principally males through occupational exposure [6].

Although contact allergy among children was previously considered to be rare, data from the past decade showed that it is common among children and that the prevalence may be increasing [7]. This is probably the result of initial undervaluation due to difficulties in testing children or because the constantly changing environment has become richer in allergens. Ni is the most common sensitizer in almost all studies pertaining to paediatric contact dermatitis, with

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frequency varying from 7.76 to 46.0% [8]. There were reports of positive reactions for Co as well as Ni in 68.0 and 71.0% of selected cases from a tertiary clinic [9].

Other elements such as gold (Au), iridium (Ir), palladium (Pd) and platinum (Pt) are deemed emerging causes of skin hypersensitivity, while aluminium (Al), beryllium (Be), copper (Cu) and titanium are considered rare allergens [10].

Ni is a nutritionally essential metal widely distributed in the environment, and it has been reported to be one of the most common causes of ACD. The prevalence of hypersensitivity to nickel in the general population is estimated to be 7–10%, with a predominance of the female sex and mean age of onset between 21 and 30 years [11]. In some professional groups, such as hairdressers, the prevalence may reach 27–38% [12].

Exposure to Ni can occur not only through contact with the skin but also by gastrointestinal absorption. In some patients with ACD, the intake of Ni with the diet may induce gastrointestinal symptoms (nausea, pyrosis, meteorism, abdominal pain, diarrhoea and constipation), in addition to typical cutaneous manifestations in areas not in contact with Ni (dermatitis, itching, urticaria) and atypical systemic manifestations (e.g. headache, chronic fatigue). This clinical picture is known as systemic nickel allergy syndrome (SNAS) or systemic contact dermatitis (SCD) [13].

10.2 Metal Hypersensitivity

One of the first reports of allergic contact hypersensitivity to metal ions was described in 1930 by Rothman, who reported the case of a 42-year-old patient suffering from a mysterious allergic response to coins [14]. Metal-induced ACD is a cell-mediated inflammatory skin condition and is categorized as a delayed-type hypersensitivity (DTH) reaction according to the Gell and Coombs classification. In order to elucidate the many basic immunological mechanisms of ACD, investigators used the experimental model of contact hypersensitivity (CHS) in mice [15]. Unlike irritant contact dermatitis (ICD), which is the clinical result of non-immunological damage to the skin by chemical and physical agents, ACD requires the activation of antigen-specific acquired immunity leading to the development of effector T cells, which mediate the skin inflammation.

Transitional metal ions are traditionally not immunogenic by themselves, due to the fact that they are too small to be recognized by the immune system's antibodies or receptors. However, contact allergens are very special due to their ability to simultaneously activate the innate immune system and form T cell epitopes. The formation of T cell epitopes requires protein reactivity of contact allergens. They behave as haptens with high immunogenic potential when in complex with cellular or matrix proteins of the skin [16]. In fact, the number of ligands and the geometry of the coordination complexes formed between metal ions and the electron-rich atoms in amino acid side chains of self-proteins (larger carrier molecules) seem to be the major factors determining the allergenicity of these metals, as well as their cross-reactivities [17]. Metal allergens mimic pathways characteristic for innate immune responses to infections. During an infection, some pathogens activate pattern recognition receptors (PRRs) such as the membrane-associated Toll-like receptors (TLRs) and the cytosolic NOD-like receptor (NLR) NLRP3, a component of the caspase-1-activating NLRP3 inflammasome. These receptors recognize components of bacteria and viruses such as DNA or RNA, bacterial cell wall components or bacterial toxins and commonly designated pathogen-associated molecular patterns (PAMPs), and they trigger the production of pro-inflammatory cytokines and chemokines. Contact allergens efficiently activate PRRs. In particular, one member of this family, TLR4, is also triggered by distinct low-molecular-weight transition metals, such as nickel, cobalt and palladium [18–20].

The interaction among a hapten-carrier complex and the immune system and the ensuing inflammatory response can be divided into two temporally and spatially dissociated phases. There is a 'sensitization (induction) phase' which describes the reaction (generally asymptomatic)

following primary application of the hapten to the skin and then an 'elicitation (effector) phase' during which the clinical symptoms of ACD are manifested upon re-exposure to the hapten. However, ACD also comprises another phase, the 'resolution phase', during which the inflammatory response progressively disappears (Fig. 10.1). This step presumably results from downregulating mechanisms including passive processes, such as the progressive clearance of the hapten from the epidermis, as well as active cellular processes, such as the activation of CD4+ regulatory T cells (Tregs). On the other hand, skin exposure to metal without primary sensitization may produce ICD.

The clinical findings of ICD and ACD can be very similar, making diagnosis difficult, but the patch test may be helpful for a correct diagnosis [22]. Eczema, the clinical expression of Ni hypersensitivity, may present with primary lesions including papules, erythematous macules and vesicles, which may coalesce to form patches and plaques. In severe forms of eczema, secondary findings may predominate, such as exudates and development of crusts. Chronic forms of eczema are often dry and characterized by thickening and desquamation of the skin (lichenification).

Sometimes, already-sensitized subjects affected by ACD may exhibit signs of elicitation of the disease following systemic exposure to the haptens (e.g. via the oral or parenteral route). This is what occurs in SNAS. In fact, both Th2 [typically associated with atopic

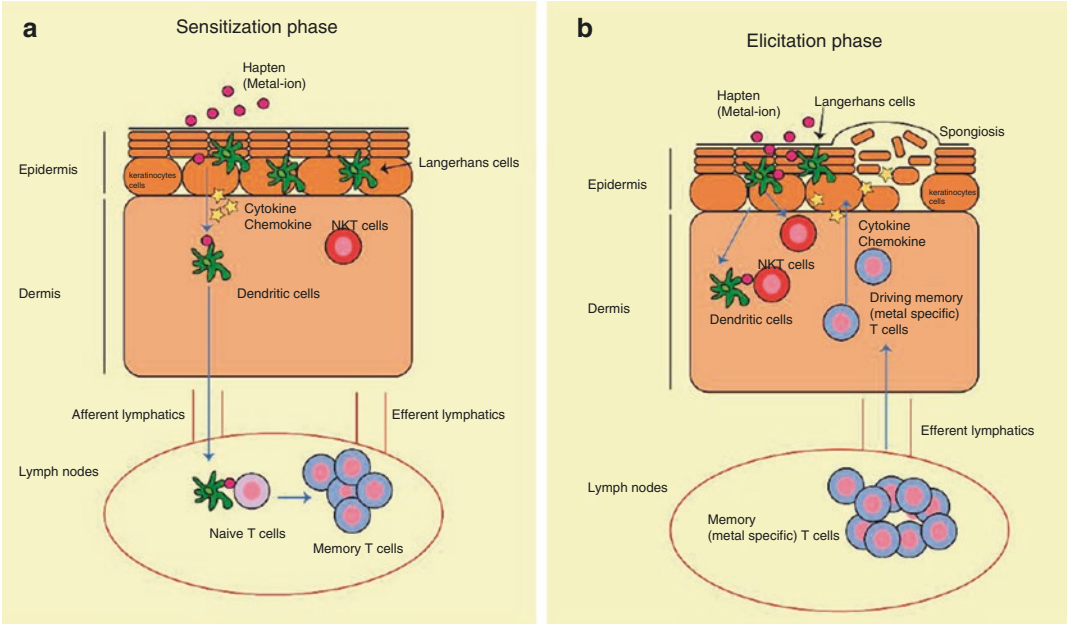

Fig. 10.1 A complex mechanism of metal ion-induced allergic contact dermatitis. (**a**) Sensitization phase in metal allergy. Step 1: Metal ions form complexes with partner molecules within the body, thereby becoming antigens. A hapten (metal ion) combines with a native protein and activates keratinocytes (KCs), cutaneous Langerhans cells (LCs) and dermal dendritic cells (DCs) through the innate immune system. Step 2: Activated DCs capture antigens, mature and migrate to the regional lymph nodes via afferent lymphatics. Step 3: Migrated DCs present antigens to naive T cells in draining lymph nodes. NK T cells affect DC functions and regulate the excessive immune response. (**b**) Elicitation phase in metal allergy. Step 1: KCs are activated by re-exposure to haptens and produce various cytokines and chemokines that activate endothelial cells and draining memory metal-specific T cells. Step 2: Infiltrated metal-specific effector T cells are activated and produce pro-inflammatory cytokines and chemokines that activate KCs and induce further inflammatory cell infiltration. Step 3: NK T cells may regulate the excessive acquired immune response caused by metal-specific effector T cells. Reprinted with permission from [21]

dermatitis (AD)] and Th1 (typically associated with ACD) responses underlie SNAS pathophysiology. It is plausible that expressed features may vary depending on the predominating immunologic milieu. While a Th2 response to Ni dominates initially, respiratory symptoms such as rhinitis and asthma, as well as cutaneous manifestations similar to AD, would be expected [23]. However, chronic exposure to Ni leads to a change in T cell expression with the development of a Th1 predominance, possibly predisposing to ACD in a similar manner to the immunologic pathophysiology seen in chronic AD patients [24].

10.3 Induction of Immunological Tolerance

The term 'tolerance' is used to define a specific immunological non-reactivity to an antigen resulting from a previous exposure to the same antigen [25]. Despite the fact that humans are widely exposed to chemicals from foods and the environment, only few subjects acquire skin sensitization to metals. This suggests that tolerance is an active process orchestrated by specialized subsets of antigen-specific lymphocytes [26].

Although factors such as the coexistence of irritation or inflammation (danger signals), co-exposures (carrier protein or adjuvant), previous UV irradiation, site and primary route of exposure are able to influence the final process leading to the development of immune tolerance, it remains unclear why some people are susceptible to hapten sensitizations, while others seem to be tolerant.

Many experimental studies in various animal models have investigated immunoregulatory mechanisms towards some haptens through different pathways such as oral tolerance, local immunosuppression induced by UV irradiation of the skin and low zone tolerance (LZT), in which epicutaneous repeated applications of very low doses of contact allergens impede the elicitation phase of CHS [27–29].

Oral tolerance refers to systemic antigen hyporesponsiveness that occurs after oral antigen administration [30]. The phenomenon of oral tolerance of cellular immune responses to metals was studied by Scheper's group, who clearly showed that feeding guinea pigs or mice with nickel- or chromium-containing foods prevented subsequent development of CHS to the respective haptens [31]. Moreover, it was showed that high doses of nickel sulphate (NiSO4) in the drinking water administrated to mice induced a complete, long-lasting immunological tolerance to nickel ions, mediated by CD4+CD8+T cells [32]. Such 'oral tolerance' is persistent, dose dependent, antigen specific and T suppressor cell mediated. Subsequently, it was observed that local administration of the typical pro-inflammatory cytokine IL-12 (but not IL-2, IFN-γ or GM-CSF) to the site of attempted immunization abrogates this orally induced tolerogenic effect and re-establishes reactivity to haptens [33].

Both the sensitization and effector phases of contact allergy are highly regulated events. This occurs via multiple mechanisms, including clonal anergy or deletion, associated with high-dose tolerance, and induction of one or more populations of Tregs, generally associated with low antigen doses [34].

The nature of the antigen-presenting cell (APC)-T cell interaction influences the balance between effector and regulatory mechanisms, determining the immunological outcome following oral antigen administration. It is well established that three distinct signals are required for an efficient T cell activation. Signal 1 is derived from recognition of MHC-peptide complexes by the TCR. Signal 2 is provided by the binding of the T cell-expressed co-stimulatory molecule CD28 to its ligands B7.1 (CD80) and B7.2 (CD86) on APC, while Signal 3 requires the secretion of cytokines by dendritic cells (DC) [35]. In the absence of any of these appropriate signals, naive T cells may be turned to a state of hyporesponsiveness to subsequent antigen encounters, also known as anergy [36], eventually leading to their death by apoptosis (deletion). This latter process of activation-induced cell death (AICD) is mediated by death receptors (FAS/FAS ligand interaction of CD4+ T cells and by TNFRII/TNF interaction of CD8+ T cells).

Treg (or T suppressor) cells play a pivotal role in the acquisition and maintenance of the T cell tolerance that is acquired through T cell contact with antigens in the absence of co-stimulatory signals. Treg cells can be broadly classified into two main groups: natural Treg cells (nTreg cells), the thymus-derived naturally occurring CD4+CD25+forkhead box protein 3 (FOXP3)+ Treg cells, and the inducible Treg (iTreg) cells, which are generated in the periphery after antigenic stimulation. iTreg cells can be further subdivided into three main subsets: (1) induced FOXP3+ Treg cells, (2) CD4+FOXP3−IL-10-producing Treg (Tr1) cells and (3) transforming growth factor (TGF)-β-expressing Th3 cells [37].

In normal adult mice or humans, CD4+CD25+ nTreg cells represent about 5–10% of the whole T cell compartment and are characterized by being highly enriched in suppressor activity, with preferential expression of high amounts of the interleukin-2 receptor a-chain (CD25). It is known that Tregs do not use a single mechanism of suppression but a variety of different modes of action to exert a suppressive effect, but some mechanisms are still not fully understood or agreed upon. Proposed mechanisms include the induced release of inhibitory/immunoregulatory cytokines (such as IL-10, TGF-β and IL-35), cytolysis (secretion of granzymes A and B), metabolic disruption mechanisms (through CD25, cAMP, adenosine, CD39 and CD73) and the targeting of DCs through CTLA-4, PD-1 or histamine receptor 2 to control priming of effector T cells by APCs. However, it is necessary to appreciate that these mechanistic pathways are not necessarily mutually exclusive [38]. Moreover, little is known of the relative contribution of the different Treg cell subsets and their mode and site of action in the control and resolution of CHS responses.

CD4+CD25+FoxP3+ T cells represent one of the largest subsets of Tregs implicated in the control of CHS responses to haptens in mice. The first evidence of such downregulatory activities of Treg cells came from a study investigating the mechanisms responsible for the 'oral tolerance' phenomenon [39]. Using in vivo models of adoptive transfer and antibody depletion of CD4+CD25+ cells, it was demonstrated that naturally occurring CD4+CD25+ T cells are instrumental for orally induced tolerance and control hapten-specific CD8+ T cell responses mediating skin inflammation [39].

Furthermore, depletion of CD4+ CD25+ T cells by in vivo treatment of mice with an anti-CD25 mAb during hapten sensitization increased the magnitude and duration of the CHS response [40]. Conversely, murine IL2-IgG2b chimeric protein suppressed the ACD reaction in association with an increase in the CD4+ CD25+ Treg cell numbers [41]. Importantly, a role for CD4+ CD25+ Treg cells in maintaining immune tolerance to skin allergens has been confirmed in humans. Cavani et al. showed that CD4+ T cells isolated from the peripheral blood of six healthy non-allergic individuals showed a limited capacity to proliferate in response to nickel in vitro. However, the responsiveness was strongly increased (by 240%) when CD25+ Treg cells were depleted [42].

As is the case with the T effector cells causing the allergic response, the regulatory function of Treg cells can also be divided into two different phases [43]. The central regulatory phase controls the expansion and differentiation of CD8 effector T cells in the skin-draining lymph node (dLN), while the peripheral phase reduces the inflammatory process generated in the skin. Whereas the effector phase of Treg cells can be studied in both mice and humans, their induction phase is difficult to study in humans in vivo. The mouse model of oral nickel tolerance provides the unique possibility to investigate both the induction and the effector phase of nickel-specific Treg cells [44].

10.4 Hyposensitization to Nickel

Ni represents the principal hapten involved in the development of ACD. Although animal models have shed light onto the pathogenesis and regulation of human contact dermatitis, the possibility of inducing specific tolerance in humans has not been investigated, owing to legal and ethical restrictions on human experiments. Indirect

evidence that seems to confirm the protective effect of oral hapten exposure in blocking the development of CHS has been provided by epidemiological studies. In fact, lower prevalence rates of contact allergy to nickel have been reported in individuals wearing orthodontic braces (oral nickel exposure) prior to ear piercing (cutaneous nickel exposure), as compared to those who underwent piercing first [45–47]. However, the results of these epidemiological observations cannot be compared with controlled animal studies, as they investigated only two ways of acquiring nickel allergy (piercing and dental braces) and were not corrected for the actual release of metal from orthodontic appliances.

More direct evidence has been provided by trials of oral hyposensitization to nickel in patients affected only by ACD. The first successful result with humans was obtained in 1987 by Sjovall, who observed less intense patch test reactions after he administered oral capsules containing 5.0 μg NiSO4/week to a selected patient group for 6 weeks [48]. Another report showed clinical improvement in 85% of patient who completed a sublingual hyposensitization treatment, but not improvement in tolerance to nickel during challenge tests [49]. Conversely, a double-blind, placebo-controlled study performed by Bagot and colleagues demonstrated that oral administration of 5 mg of NiSO4 once weekly for 7 weeks did not have an effect on clinical manifestations or nickel reactivity measured by patch tests [50].

On the basis of these experiences, the efficacy and safety of nickel hyposensitization were investigated employing low doses of nickel in patients suffering from both local contact disorders and systemic symptoms after the ingestion of nickel-containing foods. The study carried out by Schiavino et al. used a 'homoeopathic dose' of nickel (1–2 ng) in 136 of 231 patients affected by SNAS (see Table 10.1), while 95 controls were instructed to stay on the low-nickel diet. Forty-two of 136 patients (30.9%) dropped out because of lack of effectiveness. Ninety-four of the 136 (69.1%) completed the therapeutic protocol with excellent results in terms of induction of tolerance to Ni-containing food, with low incidence of side effects. In fact, 64 (47%) reported a complete remission of symptoms, 23 (16.9%) had greater than 80% improvement and 7 (5.2%) showed partial benefit. In the control group, 78/95 patients (82%) developed a relapse of preexisting systemic symptoms when Ni-containing foods were reintroduced [51].

Table 10.1 Protocol of desensitization used by Schiavino et al. [51]

1 granule every other day for 45 days
1 granule/day for 45 days
1 granule/2 granules on alternate days for 45 days
2 granules/day for 45 days
1 granule/2 granules on alternate days for 45 days
1 granule/day for 45 days
1 granule every other day for 45 days

1 granule = 0.1 ng
During the second phase (progressive dose decrease), patients gradually reintroduced nickel-containing foods [modified by reference 46]

In 2009, Tammaro et al. performed an open trial of oral hyposensitization therapy with 0.1 ng–1 mcg granules of nickel sulphate in 67 patients affected by systemic allergy to this sensitizer. All patients reported a significant benefit in regard to both cutaneous and systemic symptoms, with the reduction or absence of itching and partial or complete clearing of ACD after the first 4 weeks of treatment. In fact, 70% of the patients completed the increasing phase (10 weeks) and the maintenance phase with the following results after the reintroduction of a nickel-free diet: 67% reported a complete remission of symptoms; in 23%, a clinical improvement was noted, with the rare appearance of cutaneous or digestive symptoms of lower intensity; and three patients also reported a reduction in weight. Adverse reactions were observed in 18 patients: 12 patients with primary cutaneous dermatitis reported mild itching, and 6 patients with gastrointestinal manifestations reported digestive disorders of low intensity [52].

However, the extremely low dosage of Ni, far below that of environmental background exposure, as well as the absence of laboratory evidence of immunological modulation induced by these treatments, makes these studies only pre-

Table 10.2 Protocol of desensitization by Di Gioacchino et al. [54]

	Group 1	Group 2	Group 3	Group 4
Days	Ni dose	Ni dose	Ni dose	
1–10	1 ng/day	Placebo	Placebo	Placebo
11–20	10 ng/day	1 ng/day	Placebo	Placebo
21–30	0.1 μg/day	10 ng/day	1 ng/day	Placebo
31–40	0.5 μg/day	0.1 μg/day	10 ng/day	Placebo
41–320	0.5 μg	0.1 μg	10 ng	Placebo
	3 times a week	3 times a week	3 times a week	3 times a week

All eligible patients after 1 month of Ni-low diet were randomly assigned to one of the four groups of treatment. Nickel dose was progressively increased in 40 days from 1 ng to one of the three defined maintenance doses (10 ng, 0.1 μg and 0.5 μg) administered three times a week for a total of 12 months. In order to protect the blinding, patients randomized to lower doses received placebo during the first days of the dose increase phase

liminary observations. For these reasons, in 2010 Minelli et al. [53] published the results of an open trial using higher doses than in previous protocols. They enrolled 36 patients with SNAS: 24 were randomly assigned to the active group which received treatment and the low-Ni diet, while the remaining 12 were assigned to the control group and treated with the low-Ni diet alone. The treatment, which was performed with hard gelatin capsules containing $NiSO_4 \times 6H_2O$ at different dosages (0.1 ng, 1 ng, 10 ng, 0.1 μg, 0.5 μg), consisted of an incremental dose increase phase of nickel (0.1 ng–3 μg three times per week), followed by 12 months of maintenance (1.5 μg/week). After 4 months, prohibited foods were gradually reintroduced. NiOHT was effective in reducing symptoms and drug usage of patients with SNAS and was able to modulate inflammatory parameters.

Recently, the first randomized, double-blind, placebo-controlled trial addressing patients with a diagnosis of SNAS was published [54]. Enrolled patients had not only skin symptoms but also extracutaneous complaints, commonly gastrointestinal, which were associated with nickel consumption. Notably, no cough or headache patients received the nickel oral challenge, but since they were enrolled, they were included in the 'intention to treat' group. Patients who were both nickel patch test and nickel oral challenge positive were randomized into three groups receiving different doses of oral nickel for a year (see Table 10.2). When dietary nickel was progressively reintroduced, the group treated with the highest dose of Ni weekly showed statistically significant improvement in the cutaneous and gastrointestinal manifestations of SNAS, as assessed by subjective symptoms and individual visual analogic scale (VAS) ratings compared to placebo. The effect of NiOHT seemed dose dependent, as 1.5 μg Ni/week gave the best results, 0.3 μg Ni/week intermediate results and 30 ng Ni/week and placebo the worst results. The development of oral nickel tolerance was theorized to be due to a proliferation of nickel-specific T regulatory lymphocytes (a distinct T cell promoted by IL-10 which functions to inhibit general T cell responses).

10.5 Conclusion

Metal ions, such as nickel, cobalt, chromium and palladium, are among the most common triggers of allergic contact dermatitis. Immunologically, metal allergy is a delayed-type hypersensitivity reaction that can be divided into two phases: (1) an asymptomatic sensitization phase, characterized by subclinical innate immune activation, and (2) a clinically symptomatic elicitation phase representing the adaptive phase of allergic contact dermatitis. Several animal studies have demonstrated that extracutaneous (e.g. oral) administration of a hapten, including nickel, leads to a state of unresponsiveness that prevents subsequent hypersensitivity through skin exposure. There are real-life situations that provide insight into the

prophylactic effect of oral hapten exposure. Oral hyposensitization to nickel is a promising treatment approach for the management of nickel allergy, especially in a subset of patients with systemic nickel allergy syndrome.

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11 Assessment for Metal Allergy: Patch Testing

Radoslaw Spiewak

11.1 Fundamentals of Patch Testing

The patch test is an in vivo test to detect delayed-type hypersensitivity to haptens, including metals. In principle, it is the controlled exposure of a patient's skin to the suspected hapten in a defined amount for a predetermined time (the widely accepted standard is 2 days). After removal of the test units, repeated evaluations follow for the development of an inflammatory reaction in the skin, which typically take place after 2 days, 4–5 days and 7 days from mounting [1]. Patch test substances are applied on the patient's skin in commercially available patch test chambers. For obvious reasons, chambers made of metal should be avoided, especially when testing for contact allergy to metals. Chambers are filled with hapten preparations, which typically come in a vehicle of petrolatum (Fig. 11.1) or water (Fig. 11.2). The dosing should be as precise as possible, because too low of an amount of hapten may result in a false-negative reading, whereas too high of an amount may lead to irritant, false-positive reactions. The recommended amount is 20 µg for petrolatum-based preparations and 20 µl for aqueous solutions. Petrolatum is difficult to measure given its viscosity; thus, some training with laboratory scales is required. Water-based solutions can be aliquoted using a labora-

Fig. 11.1 Loading petrolatum-based hapten preparation into chambers of a patch test unit

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Fig. 11.2 Loading water-based hapten preparation into chambers of a patch test unit

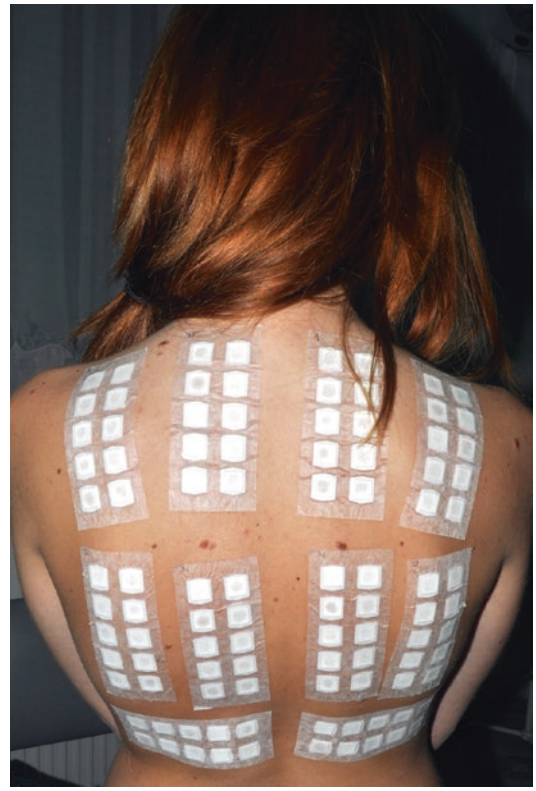

Fig. 11.3 A typical arrangement of patch test units in adults

tory micropipette; however, measuring by drops (equal ca 50 μl) is a common practice. Preparations of metals in petrolatum are relatively stable and may be preloaded and stored overnight in test units that are resealable (e.g. IQ Ultra or IQ Ultimate chambers). In contrast, after loading liquid hapten preparations, chambers should be placed immediately on the patient's back, as they must not dry before placement. The typical arrangement of patch test units is shown in Fig. 11.3 (adults); in small children, transverse placement may prove more practical (Fig. 11.4). After attaching the test units on the patient's back, each individual chamber should be firmly pressed in order to ensure good contact and hence penetration into the skin with an even distribution of the hapten in the whole exposure area. The test units are removed after 2 days. Appropriate skin markings allow for proper assignment of emerging reactions to responsible haptens (Fig. 11.5). According to recent guidelines, the recommended observation time is 7 days; however, positive reactions may emerge later than this in some patients.

The widely accepted system for recording reaction intensity is the International Contact Dermatitis Research Group (ICDRG) scale, described in Table 11.1 and shown in Fig. 11.6. It must be stressed that the intensity of reaction does not necessarily reflect the relevance of a given hapten for the present disease. The intensity of patch test reaction as expressed in the ICDRG score is dependent on the concentration of hapten in the test substance, area of the test chamber used, dose per surface unit and bioavailability from a chosen vehicle. Clinical disease, aside from the concentration and dose of hapten per exposed surface, also depends on the size of the exposed area, frequency and duration of repeated exposures, skin thickness and physiological status of the skin, among other factors. In the case of dental implants and endoprostheses,

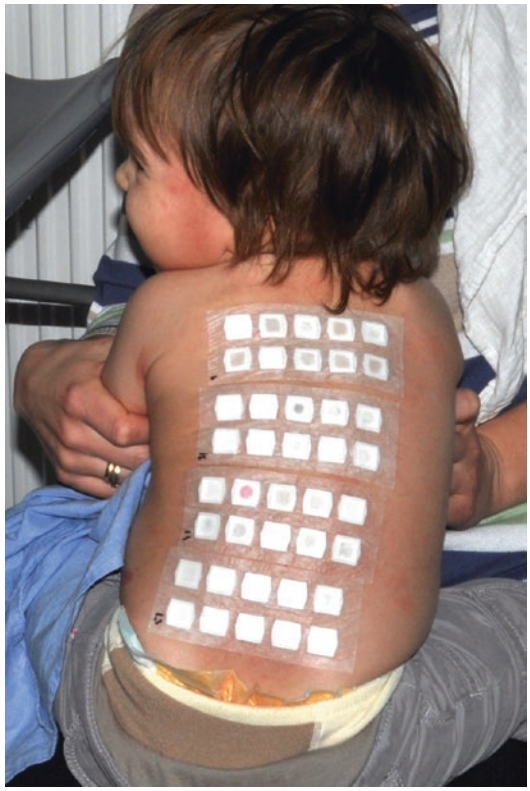

Fig. 11.4 Transverse placement of test units may prove more practical in small children

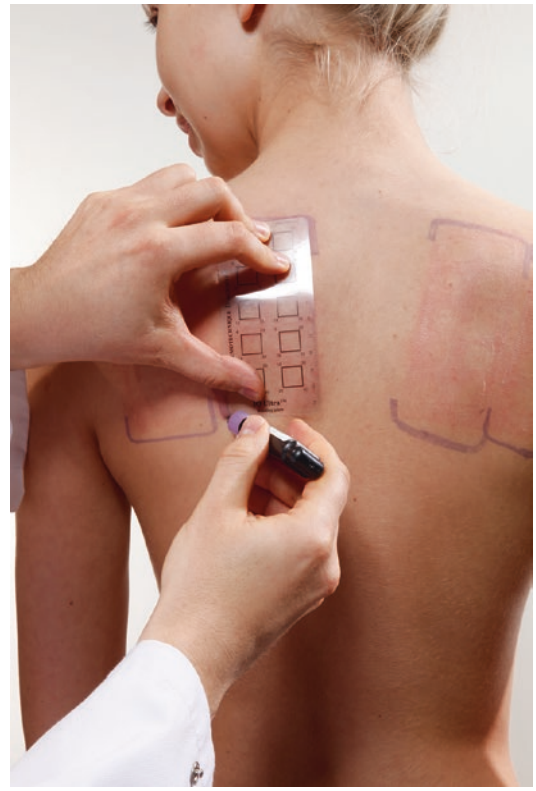

Fig. 11.5 Marking positions of patch test units of the patient's back immediately after their removal

Table 11.1 Notation of patch test results according to the ICDRG

Notation	Description	Interpretation and comments
–	Negative: no visible reaction in the tested area	All haptens with negative test results should be listed in the result form
?+	Faint, non-palpable erythema	Doubtful reaction
+	Palpable erythema—moderate oedema or infiltrate, papules not present or scarce, vesicles not present	Weak reaction
++	Strong infiltrate, numerous papules, vesicles present	Strong reaction
+++	Coalescing vesicles, pseudo-bullae or ulceration	Extreme reaction
IR	Irritant reaction: limited to the exposed area, lack of infiltrate (oedema may be present), 'common reaction' with homogeneous erythema without infiltration, 'poral reaction' with punctate erythema, sometimes slightly papular or haemorrhagic, 'pustular reaction' with one or numerous pustules, possibly efflorescences other than papules and vesicles	This kind of reaction may cause relevant problems upon interpretation
NT	Not tested	Has to be clearly marked in case of unavailability (or skipping) of a test substance that is listed in a standard form

the route of exposure and bioavailability of the hapten is completely different. Therefore, assessing for the clinical relevance of a positive patch test reaction is as important as the execution of patch testing itself. Several systems for grading the clinical relevance of varying degrees of complexity have been proposed, but none are generally accepted like the ICDRG score. In practice,

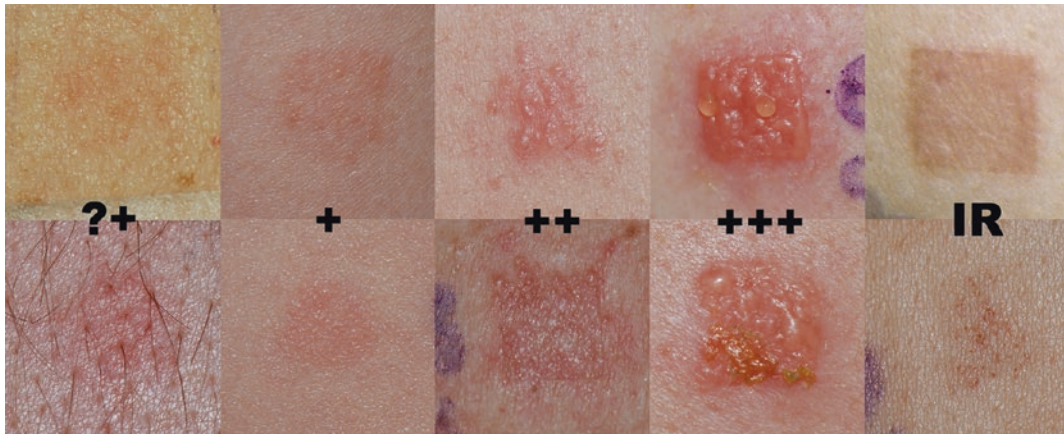

Fig. 11.6 The spectrum of patch test reactions. Explanations for the symbols are given in Table 11.1. Irritant reactions depicted on the *right-hand side* of the composite picture are a 'common irritant reaction' manifesting as homogeneous erythema without infiltration (*top*) and a 'poral reaction' with punctate erythema (*bottom*). (Reproduced with permission from [2])

Table 11.2 The practical CODEX system for assigning relevance to positive allergic reactions

Code	Definition
C (current)	Patient has been exposed to the hapten prior to the current episode of dermatitis, improvement of the disease after cessation of exposure
O (old)	Past episode of dermatitis from exposure to the hapten, no present exposure or no reactions to present exposures
D (don't know)	Relevance difficult to assess, no traceable relationship between the hapten and present disease
E (exposed)	History of previous exposures which, however, seemed not to cause dermatitis
X (cross-reaction)	Positive due to structural similarity with other haptens of actual relevance

good results can be achieved by combining two relatively simple and mutually complementary systems: the modified CODEX grading system and the North American Contact Dermatitis Group (NACDG) system. The CODEX system, presented in Table 11.2, is a modification of the original COADEX system ([3], modified by [4]). In the present modification, the letter 'A', which originally stood for 'active sensitization', has been omitted in the mnemonics for better usability and less confusion. Active sensitization during patch testing, though not impossible, is very difficult to judge in individual cases and extremely rare even among late patch test reactions [5]. Most importantly, it also does not provide information regarding the question of relevance of a positive reaction. Whenever feasible, current relevance (CODEX: C) can be further graded as definite (positive use test with the suspected item or a positive patch test to the object or product), probable (the presence of the hapten in patient's skin products could be verified, and clinical presentation is consistent with the exposure) or possible (patient was exposed to circumstances in which skin contact with materials known to contain the hapten was likely to occur), in line with the North American Contact Dermatitis Group relevance scoring system [6].

11.2 Problems and Pitfalls When Patch Testing with Metals

Common problems with patch tests to metals include limited accessibility of test material and difficulties with reading and interpreting the results due to intrinsic irritant properties of many metals. In an adult population heavily exposed to metals (metal workers), non-allergic irritant reactions constituted 6.5% of all patch test reactions seen to nickel sulphate 5% pet., 13% of reactions

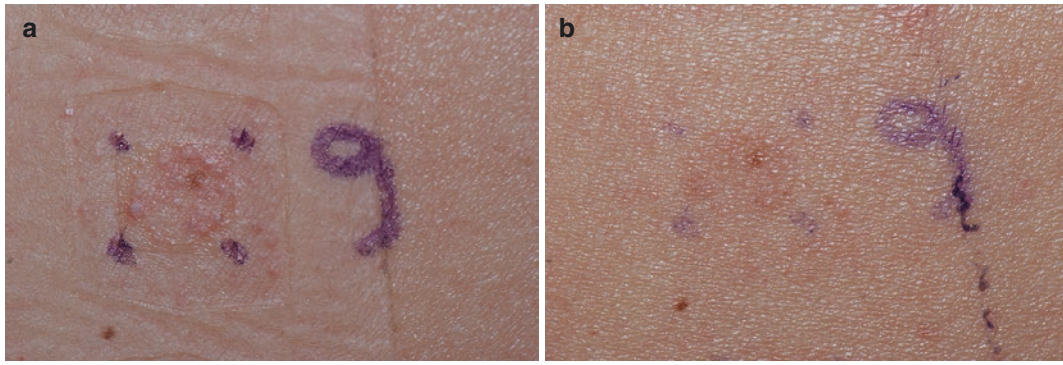

Fig. 11.7 (**a**) Irritant reaction of pustular type to zinc chloride 2% pet. immediately after removal of the patch test (after 2 days of occlusion). (**b**) The same test site 1 day later. Note the apparent 'decrescendo' pattern indicating that healing processes had begun immediately after removal of the irritant

to potassium dichromate 0.5% pet. and 18.3% of reactions to cobalt chloride 1% pet. [7]. The authors divided non-allergic reactions to metals into three distinct types: (1) the 'common irritant reaction' manifesting as homogeneous redness without infiltration; (2) the 'poral reaction' with punctate erythema, sometimes slightly papular or haemorrhagic, presenting as small dots distributed within the test area; and (3) the 'pustular reaction' with one or numerous pustules in the exposed area. Examples of these reactions are shown in Fig. 11.6 (common irritant reaction in the upper right corner, poral reaction in the lower right corner) and Fig. 11.7a, b (pustular reaction). Fischer and Rystedt observed that poral reactions were more reproducible than the other irritant reactions, which they ascribed to a constitutional, non-allergic susceptibility to metals in such individuals. Storrs and White [8] studied clinical and microscopic features of irritant reactions to cobalt and found that, regardless of the 'petechial' appearance and regular spacing suggesting involvement of hair follicles, epidermal inflammation and necrosis in such reactions actually surround the acrosyringium, i.e. the intraepidermal spiral duct of the eccrine sweat gland; over time, individual reactions may become confluent to form a purpuric-appearing plaque. The authors stressed that such reactions are neither follicular nor petechial, nor allergic. This problem seems more frequent in children. Marcussen [9] observed that patch test reactions to nickel presenting as clusters of small erythematous dots at regular spaces were predominantly seen in children with no convincing history of nickel allergy; moreover, such reactions could not be confirmed in intradermal testing or patch testing repeated after a longer time interval. He suggested, therefore, that these were primary irritant reactions due to peculiarities of the epidermal barrier that disappear around 8 years of age, which may correspond to the individual susceptibility mentioned by Fischer and Rystedt [7]. Not all physicians seem aware of these phenomena, which may in part explain higher patch test positivity rates reported among younger children. In a multicentre study based on the work of paediatric or general allergists, rather than dermatologists [10], patch tests to nickel sulphate 5% pet. were reported positive in 35.9% of 7–8-year-olds versus 19.4% of 16–17-year-olds; similar trends also were seen for cobalt chloride 1% pet. (9.7% versus 6.5%) and potassium dichromate 0.5% pet. (6.8% versus 3.2%).

In summary, one must be aware of the risk of irritant patch test reactions to metals that may occur in any age group, especially younger ages. Nevertheless, true allergic reactions to metals do occur in infants and children: rates of ascribed clinical relevance out of all positive patch tests to nickel sulphate (200 μg/cm^2) varied from 4.8% (just 1 out of 26) in Danish infants at 3–18 months of age [11] to 69.4% in Danish children 12–16 years old [12]. Among Brazilian children

0–12 years old, the relevance rate was 82.8% of all positive reactions to nickel sulphate 5% pet. [13]. Of all reactions to potassium dichromate 54 μg/cm^2 and cobalt chloride 20 μg/cm^2 seen among Danish teenagers (12–16 years old), 16.7% and 58.5%, respectively, were assessed as clinically relevant [12].

Aside from nickel, cobalt and chromium which are present in most baseline series, as well as a few other metals like palladium or gold, there are scarce epidemiological data or clinical experience on most remaining metals, partly due to the limited availability of patch test substances. The situation has partly improved after a commercial metal series for patch testing was introduced. Table 11.3 collates presently available patch test preparations of metals, while Table 11.4 summarizes our experience with commercial preparations. Despite continuous development in the field, some metals frequently found in implanted

Table 11.3 A summary of commercially available patch test preparations for metals as of 2016

Metal	Preparation	Cat. no.
Aluminium [Al]	Aluminium as is (powder)	A-021
	Aluminium (III) chloride hexahydrate 2% pet.	A-022
	Aluminium hydroxide 10% pet.	A-038
Beryllium [Be]	Beryllium (II) sulphate tetrahydrate 1% pet.	B-044
Cadmium [Cd]	Cadmium chloride 1% aq.	C-001
Copper [Cu]	Copper (I) oxide 5% pet.	C-021
	Copper (II) sulphate pentahydrate 2% pet.	C-022
Gallium [Ga]	Gallium (III) oxide 1% pet.	G-007
Gold [Au]	Gold (I) sodium thiosulphate dihydrate 0.5% pet.	G-005A
	Gold (I) sodium thiosulphate dihydrate 2% pet.	G-005B
	Potassium dicyanoaurate (I) 0.1% aq.	P-015
Indium [In]	Indium 1% pet.	I-015
	Indium (III) chloride 10% aq.	I-011
	Indium (III) sulphate 10% aq.	I-013
Iridium [Ir]	Ammonium hexachloroiridate (IV) 0.1% aq.	A-034
	Iridium (III) chloride trihydrate 1% pet.	I-012
	Iridium 1% pet.	I-014
Iron [Fe]	Ferric chloride 2% pet.	I-016
Lead [Pb]	Lead (II) acetate trihydrate 0.5% aq.	L-007
	Lead (II) chloride 0.2% aq.	L-008
Manganese [Mn]	Manganese chloride 2% pet.	M-031
Mercury [Hg]	Mercury 0.5% pet.	M-005
	Mercury (II) chloride 0.1% pet.	M-004
	Mercury (II) amidochloride 1% pet.	M-022
	Phenyl mercuric acetate 0.01% aq.	P-008
Molybdenum [Mo]	Molybdenum 5% pet.	M-030
	Ammonium molybdate (VI) tetrahydrate 1% aq.	A-035
	Molybdenum (V) chloride 0.5% pet.	M-038
Niobium [Nb]	Niobium (V) chloride 0.2% pet.	N-008
Palladium [Pd]	Palladium (II) chloride 2% pet.	P-001
Platinum [Pt]	Ammonium hexachloroplatinate (IV) 0.1% aq.	A-010
	Ammonium tetrachloroplatinate (II) 0.25% aq.	A-013
	Sodium tetrachloropalladate (II) hydrate 3% pet.	S-017
Rhodium [Rh]	Rhodium (III) chloride hydrate 2% pet.	R-013
Ruthenium [Ru]	Ruthenium 0.1% pet.	R-012
Silver [Ag]	Silver nitrate 1% aq.	S-007
Tantalum [Ta]	Tantalum 1% pet.	T-047

Table 11.3 (continued)

Metal	Preparation	Cat. no.
Tin [Sn]	Tin 50% pet.	T-008
	Tin (II) oxalate 1% pet.	S-014
	Stannous chloride 1% pet.	S-013
Titanium [Ti]	Titanium (III) nitride 5% pet.	T-039
	Titanium dioxide 10% pet.	T-040
	Titanium (III) oxalate decahydrate 5% pet.	T-041
	Calcium titanate 10% pet.	C-049
	Titanium 10% pet.	T-042
Tungsten [W]	Tungsten 5% pet.	T-043
	Sodium tungstate dihydrate 2% aq.	S-019
Vanadium [V]	Vanadium 5% pet.	V-002
	Vanadium (III) chloride 1% pet.	V-003
	Vanadium (V) oxide 10% pet.	V-005
Zinc [Zn]	Zinc 2.5% pet.	Z-001
	Zinc chloride 1% pet.	Z-007B
Zirconium [Zr]	Zirconium (IV) chloride 1% pet.	Z-008
	Zirconium dioxide 0.1% pet.	Z-009

medical devices, or other metal alloys, are still not available commercially (e.g. barium, hafnium, yttrium), although they seem to have at least some sensitizing potential based on their chemical properties and casuistic clinical observations. Moreover, new metals may be put into use in medical devices, e.g. a recent inclusion of cerium (Ce) in dental implant alloys. In such cases, custom-made preparations seem the only option for diagnostic work-up. A few examples of custom-made patch test preparations used in our clinic are given in Table 11.5; since their initial creation, some of these have become available as commercial preparations.

When selecting the formula and vehicle for patch test substances, de Groot's excellent reference book [14] and an extensive literature search are obligatory. Irritant properties of metals are a well-known problem that may bias patch test outcome. Concentrations of metals in patch test preparations should not be so high as to cause irritant reactions; on the other hand, too low of a concentration of the hapten bears the risk of doubtful or false-negative reactions. With scarce evidence, the chosen concentration is not always optimal for diagnosis. In 2010, the author had the opportunity to patch test a group of healthy soldiers with newly available commercial preparations of metals. One of the outcomes was a series of inflammatory reactions with pustules, rather than vesicles, to zinc chloride pet. 2%, with no traceable relevance (Fig. 11.7a, b). Irritancy due to too high of a concentration seemed a possible explanation. After the concentration was reduced to 1%, this problem never occurred again; however, irritant reactions still have occurred (compare Table 11.4). Nevertheless, further decreasing the concentration might result in an increased risk of false-negative reactions. In routine testing, the proven way around the present risk of false-positive reactions is a repeated, careful reading of patch test reactions by an experienced dermatologist or allergist, with photodocumentation of the reaction and reanalysis of the photographs in chronological order in case of any doubt. Such time series may reveal various patterns. A clear decrease in the intensity of inflammation on subsequent readings (the so-called 'decrescendo' pattern in analogy to a decrease in volume of a musical passage) reflects a rapidly healing process and speaks in favour of an irritant reaction or a false-positive patch test result (Fig. 11.7a, b). Sharply demarcated reactions reflecting the shape of the test chamber or reactions that occur only in a part of the occluded area also suggest an irritant reaction. On the other hand, an inflammatory

Table 11.4 An overview of patch test results to metals in patients referred to our clinic for the diagnosis or prediction of allergy to implanted metal devices—results with commercially available test substances

Hapten	Formula	Vehicle, conc.	Cat. no.	Tested	Irritant (IR)	Doubtful (?+)	Positive (+)	Positive (++)	Positive (+++)	Relevant
Aluminium [Al]	Aluminium powder	100% (metal powder)	A-021	39	0	0	1	0	0	1
	Aluminium chloride hexahydrate	2% pet.	A-022	66	0	2	1	0	0	1
Cadmium [Cd]	Cadmium chloride	1% aq.	C-001	39	0	0	0	0	0	0
Chromium [Cr]	Potassium dichromate	0.5% pet.	P-014A	244	7	31	75	2	0	33
Cobalt [Co]	Cobalt (II) chloride hexahydrate	1% pet.	C-017A	243	44	27	61	6	1	30
Copper [Cu]	Copper sulphate	2% pet.	C-022	107	8	7	11	0	0	3
	Copper (I) oxide	5% pet.	C-021	50	0	7	3	0	0	1
Gold [Au]	Gold sodium thiosulphate	0.5% pet.	G-005A	66	0	1	9	2	0	4
	Gold sodium thiosulphate	2% pet.	G-005	124	2	8	36	6	0	6
	Potassium dicyanoaurate	0.1% aq.	P-015	39	0	2	0	0	0	0
	Ammonium hexachloroiridate	0.1% aq.	A-034	39	0	1	0	0	0	0
Indium [In]	Indium sulphate	10% aq.	I-013	39	0	1	2	0	0	0
	Indium	1% pet.	I-015	38	0	1	1	0	0	0
	Indium (III) chloride	10% aq.	I-011	39	0	1	3	0	0	0
Iridium [Ir]	Iridium	1% pet.	I-014	40	0	1	0	0	0	0
	Iridium (III) chloride trihydrate	1% pet.	I-012	40	0	0	1	0	0	0
Iron [Fe]	Ferric chloride, iron (III) chloride	2% pet.	I-016	52	3	7	12	1	0	6
Lead [Pb]	Lead chloride	0.2% aq.	L-008	39	0	0	0	0	0	0
	Lead acetate trihydrate	0.5% aq.	L-007	39	0	0	0	0	0	0
Manganese [Mn]	Manganese (II) chloride	2% pet.	M-031	39	2	6	8	0	0	0

Mercury [Hg]	Mercury	0.5% pet.	M-005	60	0	0	2	0	0	0
	Mercuric chloride	0.1% pet.	M-004	226	0	9	17	0	0	1
	Mercury ammonium chloride	0.1% pet.	M-022	39	0	0	1	0	0	0
Molybdenum [Mo]	Molybdenum	5% pet.	M-030	41	0	1	0	0	0	0
	Ammonium molybdate tetrahydrate	1% aq.	A-035	39	0	0	0	0	0	0
Nickel [Ni]	Nickel sulphate hexahydrate	5% pet.	N-002A	244	0	13	56	25	5	45
Palladium [Pd]	Palladium chloride	2% pet.	P-001	244	1	18	34	11	0	15
	Sodium tetrachloropalladate (II) hydrate	3% pet.	S-017	108	0	25	26	6	0	8
Platinum [Pt]	Ammonium hexachloroplatinate	0.1% aq.	A-010	39	0	0	0	0	0	0
	Ammonium tetrachloroplatinate	0.25% aq.	A-013	39	0	0	1	0	0	0
Silver [Ar]	Silver nitrate	1% aq.	S-007	69	0	3	2	0	0	1
Tin [Sn]	Tin	50% pet.	T-008	59	0	1	0	0	0	0
	Tin (II) oxalate; Stannous oxalate	1% pet.	S-014	40	0	1	1	0	0	0
	Stannous chloride	1% pet.	S-013	120	4	13	49	1	0	1
Titanium [Ti]	Titanium nitride	5% pet.	T-039	47	0	0	1	0	0	1
	Titanium dioxide	10% pet.	T-040	70	0	2	0	0	0	0
	Titanium oxalate decahydrate	5% pet.	T-041	49	0	6	2	0	0	1
	Calcium titanate	10% pet.	C-049	51	0	1	0	0	0	0
	Titanium	10% pet.	T-042	48	0	2	0	0	0	0
Tungsten [W]	Tungsten	10% pet.	T-043	43	0	1	0	0	0	0
Vanadium [V]	Vanadium	5% pet.	V-002	39	1	1	0	0	0	0
	Vanadium (III) chloride	1% pet.	V-003	39	1	2	10	0	0	0
Zinc [Zn]	Zinc chloride	1% pet.	Z-007	128	15	15	30	0	0	9
	Zinc	2.5% pet.	Z-001	48	0	0	0	0	0	0
Zirconium [Zr]	Zirconium chloride	1% pet.	Z-008	44	0	0	1	0	0	0

Table 11.5 An overview of patch test results to metals in patients referred to our clinic for possible allergy to implanted metal devices—results with custom-made test substances

Hapten	Chemical formula	Vehicle, conc.	Tested	Irritant	Doubtful (?+)	Positive (+)	Relevant
Barium [Ba]	$BaSO_4$	2% pet.	36	0	2	0	0
Beryllium [Be][a]	$BeSO_4$	1% pet.	21	0	0	4	1
Hafnium [Hf]	$Hf(SO_4)_2$	1% pet.	29	0	1	0	0
	$Hf(SO_4)_2$	2% pet.	29	0	2	1	0
Niobium [Nb][a]	$NbCl_5$	2% pet.	39	1	9	7	2
Tantalum [Ta][a]	$TaCl_5$	1% pet.	37	1	3	3	1
Yttrium [Y]	YCl_3	2% pet.	38	0	6	9	1

[a]The above haptens were not available commercially while collecting the data. At the moment of completing this chapter, three of the above haptens are already available (Chemotechnique Diagnostics): niobium chloride 0.2% pet. (N-008), beryllium (II) sulphate tetrahydrate 1% pet. (B-044) and tantalum 1% pet. (T-047)

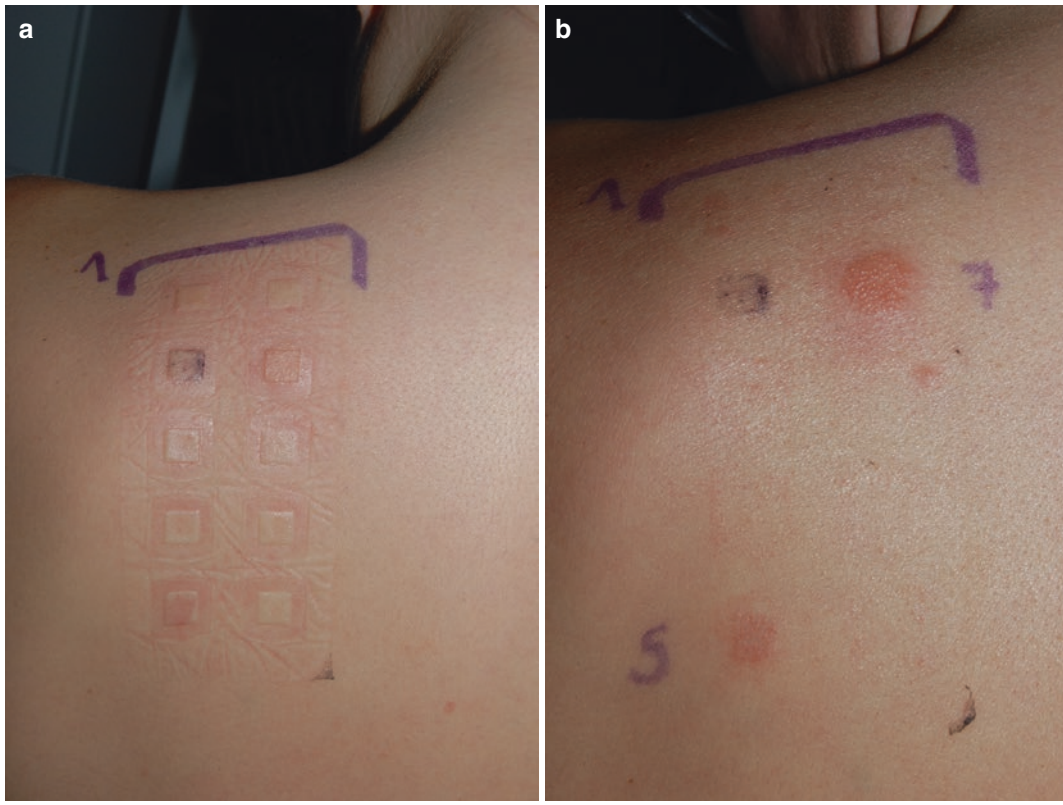

Fig. 11.8 (**a**) True allergic reactions may not yet be seen after 2 days: at the moment of removing patch tests units, only slight erythema can be seen, insufficient for recognizing any definite reaction. (**b**) One day later, a + reaction to cobalt (II) chloride hexahydrate 1% pet. (position 5) and a ++ reaction to nickel sulphate hexahydrate 5% pet. are clearly visible, consistent with the 'crescendo' pattern reflecting the progression of allergic processes triggered by the haptens

reaction covering entirely, or even expanding beyond the area of occlusion, blurry edges and increasing intensity on subsequent readings (the so-called 'crescendo' pattern) are suggestive of a true allergic reaction (Fig. 11.8a, b). However, mixed patterns may also emerge. In case of any doubt, when the result of patch testing has a potentially significant impact (such as deciding

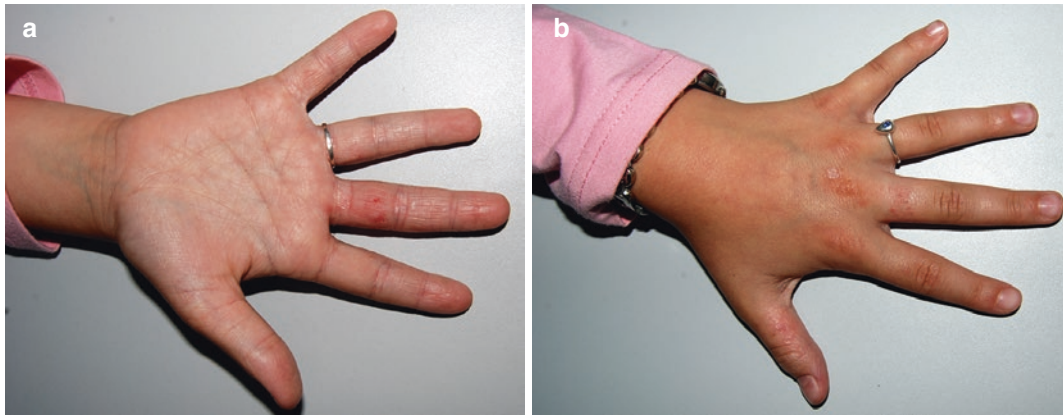

Fig. 11.9 (**a**) Palmar aspect of the right hand of Patient 1 with dermatitis most pronounced on the proximal phalanx of her middle finger, where she typically wore the cobalt- and nickel-containing ring. The ring was moved to the adjacent finger only for the picture. (**b**) Dorsal aspect of the left hand of Patient 1. The ring was moved from the middle finger onto the adjacent finger just before taking the picture

whether to use or remove an implant or artificial joint), patch testing with a dilution series of the hapten in question should be undertaken in the patient, along with a group of healthy controls whenever feasible.

11.3 Diagnostic Work-Up and Assessment of Relevance: Examples from Practice

The cases below illustrate the practice of patch testing to metals with a focus on the discussion of clinical relevance of positive patch tests. Unfortunately, unlike fashion jewellery, implants and prostheses are in most cases difficult to remove in order to see if the patient's problems would improve. The readers are kindly asked to bear in mind the risk of misinterpreting the facts in each individual case and to use their own critical judgement.

11.3.1 Patient 1: Nickel and Cobalt Allergy in a Child

A 10-year-old patient had suffered from hand eczema for the preceding 3 years. Initially, only the dominant right hand was involved, but eczema of the left hand appeared 2 years later. She had been a compulsive finger sucker, nail biter and hand washer, washing her hands around 20 times daily with hot water and abundant soap. The parents noted that the eczema had started under and next to the costume jewellery rings that the child had been wearing since the age of 4 years old (Fig. 11.9a, b). Patch testing with a commercial baseline series (Chemotechnique) revealed positive reactions to nickel sulphate hexahydrate 5% pet. (N-002A, ICDRG: +, CODEX: C) and cobalt chloride hexahydrate 1% pet. (C-017A, ICDRG: +, CODEX: C), deemed as clinically relevant based on the pronounced eczema around the rings and the presence of both nickel and cobalt in both of these (positive Chemo Nickel Test and Chemo Cobalt Test). Ultimately, allergic contact dermatitis to nickel and cobalt with irritant contact dermatitis of the hands due to the child's compulsive behaviour was diagnosed.

11.3.2 Patient 2: Hand Dermatitis to Aluminium

A 49-year-old patient complained of hand eczema that had started 3 months earlier and was gradually worsening. He had a history of past episodes of foot dermatitis or eczema dispersed over the trunk, which were transient and never motivated him to seek a doctor. The present hand eczema, however, became aggravating to the extent that

his work was made impossible. For the last 8 years, he had been working as a sales representative delivering men's suits and trousers to garment stores. His work involved handling clothes hangers, which were made of aluminium or (less frequently) stainless steel. Patch testing with a commercial baseline series, textile finishes and dyes and a metal series (Chemotechnique), along with samples of garment textiles and plastic protective bags for the cargo, revealed allergy to aluminium powder (Chemotechnique, A-021, ICDRG: +, CODEX: C) and aluminium chloride hexahydrate 2% pet. (A-022, ICDRG: +, CODEX: C). The patient was advised to always handle his cargo using protective gloves, which resulted in considerable improvement within 2 weeks, thus confirming the clinical relevance of aluminium allergy for his hand eczema. He also reacted to textile dyes Disperse Blue 3 and Disperse Blue 106 (both ICDRG: + and CODEX: O), which in light of the distribution pattern could be causative of his past episodes of dispersed dermatitis. He did not, however, react to any of the textile samples taken from the suits he was handling at his present job.

11.3.3 Patient 3: Allergic Contact Dermatitis to Gold

A 52-year-old office clerk complained of a 4-month history of eczema of her right hand and both eyelids. Her past history did not give any clues as to a possible provoking agent, except that she had noticed a slight irritation around her gold wedding ring when washing dishes without gloves. She assumed that the problem was caused by detergent collecting under the ring and removed it 2 days before the first visit. She had not noticed any symptoms of metal intolerance in the past. On patch testing, she developed positive reaction to gold sodium thiosulphate 2% pet. (Chemotechnique, G-005B, ICDRG: +, CODEX: C), with no other relevant positive reactions. She was instructed not to wear any gold jewellery, and her dermatitis both on the hand and eyelids cleared within 2 weeks without a need for further treatment. Current clinically relevant positive patch tests to gold seem relatively rare; however, these relevance rates are not much different from other common metals. Those who notice intolerance of gold tend to remove their gold jewellery, so it is more probable to find past relevance rather than current relevance for positive patch tests to gold [15].

11.3.4 Patient 4: Persistent Patch Test Reaction to Gold

A 5-year-old boy had suffered since the age of 1 from exfoliative dermatitis of the palms and soles with periodic spread of eczema to other body sites. The parents did not suspect any provoking or aggravating factors other than 'running on all fours on the carpet floor'. Patch tests with the baseline series were carried out as allergic contact dermatitis was part of the differential diagnosis. No history of metal intolerance was given by the parents; however, gold was added to the test programme as the child was from a community in which the abundance of gold in daily objects was used for showing social status. Patch tests revealed a clinically relevant allergy to *Dermatophagoides* mix 30% pet. (Chemotechnique Mx-21C, ICDRG: +, CODEX: C) and propolis 10% pet. (P-022, ICDRG: +, CODEX: C). There was also a positive patch test reaction to gold sodium thiosulphate 2% pet. (G-005B, ICDRG: +, CODEX: E). This reaction was deemed an immunological remnant from previous exposure, as the parents described a custom in their community of each newborn being given a gold necklace with a pendant. The boy had received a golden teddy bear pendant, which he used to suck on 'very eagerly'. As a precaution, the parents were instructed to isolate the child from direct contact with gold objects. A month later, they reappeared stating that, after patch testing, all positive reactions on the boy's back cleared up within 2 weeks, and the skin greatly improved with appropriate treatment and removal of the carpet and propolis-containing products from the household. However, the patch test reaction to gold re-emerged a month later with a parallel recurrence of eczema of the hands and feet. In the patch test site to gold, a dermal-type infiltrate was present (Fig. 11.10). The reaction was still present during a last check-up

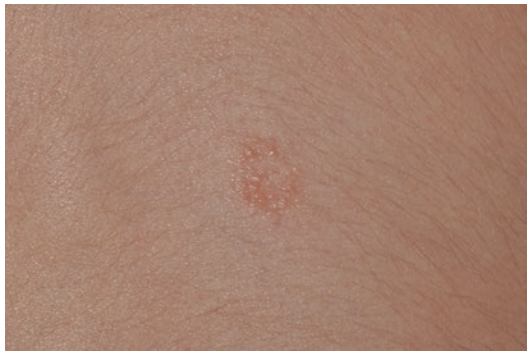

Fig. 11.10 Persistent reaction to gold in Patient 4 still present 7 months after the patch test

7 months after the test, although the eczema gradually resolved by this time. It is unclear whether the child got ahold of some gold objects to provoke the relapse or if it was a kind of late recall phenomenon due to exposure from patch testing. The temporary clearance after patch testing seemed to speak against the latter possibility, but both alternatives would suggest a current relevance (CODEX: C). Long-lasting reactions to gold after patch testing are a known phenomenon [16] that may distress patients and parents.

11.3.5 Patient 5: Photoallergic Dermatitis to Copper

A 34-year-old hairdresser complained of 'sun allergy' manifesting as dermatitis of the face and dorsal aspects of her hands that appeared on the second day of her summer vacation at the seaside and persisted over the rest of her stay. This problem had appeared on vacation for the second year in a row. In the past, she had also experienced a few episodes of skin rash provoked by cosmetics. The patient was patch tested to the baseline series, cosmetic series, hairdressing series (Chemotechnique) and her own cosmetics, which resulted in a confirmation of contact allergy to 4-phenylenediamine (P-006, ICDRG: +, CODEX: C) and 2-bromo-2-nitropropane-1,3-diol (Bronopol) 0.5% pet. (B-015B, ICDRG: +, CODEX: C). Both haptens were present in products used in her hair salon. It seemed, however, that these sensitizations could not explain her dermatitis while on holiday. She went on to undergo photopatch testing, during which she developed some flagellate erythema with a few wheals on the irradiated area, while no definite photoallergy to any of the agents from the photopatch series could be confirmed. Upon repeat questioning, the only conspicuous event that took place shortly before the first episode of her 'sun allergy' was the implantation of a copper-based IUD (Multiload Cu 375), which she still had in place. In order to clarify this, a second photopatch test was undertaken that revealed photoallergic reactions to copper (I) oxide 5% pet. (C-021, ICDRG: +, CODEX: C) and copper (II) sulphate 2% pet. (C-022, ICDRG: +, CODEX: C). The confirmation of clinical relevance came after she had the IUD removed: she did not experience any skin problems during the following summer.

11.3.6 Patient 6: Allergy to Titanium

A 62-year-old office clerk needing a hip replacement was referred for patch testing with a metal series because of a history of jewellery and wristwatch intolerance. Patch tests revealed no reaction to 'common metals' (Ni, Co, Cr); however, she developed a positive reaction to titanium oxalate 5% pet. (Chemotechnique T-041, ICDRG: +, CODEX: C) and a weak, macular, slightly infiltrated response to titanium nitride 5% pet. (T-039, ICDRG: ?+, CODEX: C). No visible reaction was present to titanium dioxide 10% pet. (T-040), calcium titanate 10% pet. (C-049) or titanium 10% pet. (T-042). Only after hearing about the results, the patient mentioned that 7 years earlier she had had a partial gastrectomy for a perforating stomach ulcer. After the surgery, she suffered from persistent nausea and vomiting. Because the symptoms continued, surgical revision was undertaken a few weeks later, after which she quickly recovered. The patch test result reminded her that titanium staples were used during the gastrotomy, and they were removed at the revision because the stomach wall had already healed and they were no longer needed. This seems to speak in favour of past clinical relevance of allergy to titanium in this patient. On patch testing, she also reacted to zinc chloride 1% pet.

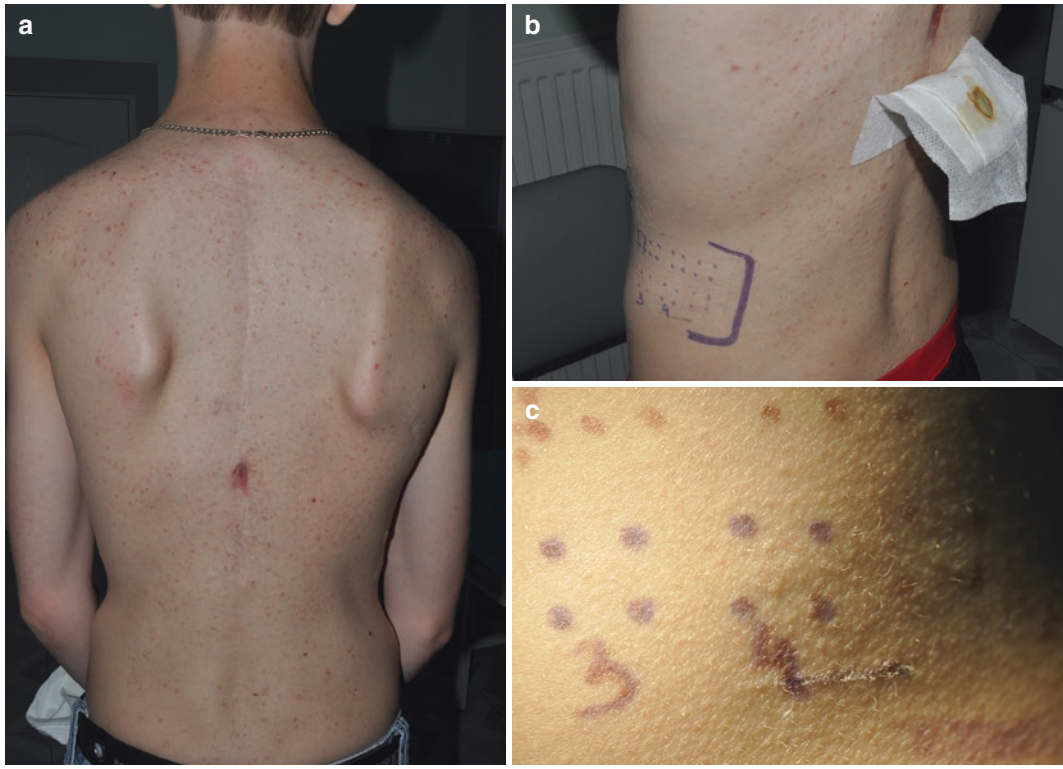

Fig. 11.11 (**a**) Patient 7 before patch testing. A scar along the spine with a closed fistula can be seen. (**b**) Positive patch test reaction to custom-made niobium (V) chloride 2% pet. (position 3) on the third day of the test. The 'dermal'-type reaction is characterized by a dominating infiltrate and lack of eczema. Note the putrid discharge from the fistula. (**c**) Positive reaction to custom-made tantalum (VI) chloride 2% pet. (position 4) on the fourth day of the test. 'Dermal' patch test reactions are difficult to capture on camera; low-angle, tangential illumination may help with this regard

(Z-007, ICDRG: +, CODEX: D), stannous chloride 1% pet. (S-013, ICDRG: ++, CODEX: D) and a preparation of niobium (V) chloride 2% pet. (ICDRG: +, CODEX: D), with which no causal relationship with her symptoms could be found.

11.3.7 Patient 7: An Abscess with Fistula in a Protracted Spine Stabilization of Scoliosis

An 18-year-old student had undergone an orthopaedic stabilization 2 years earlier for his pronounced scoliosis and chronic severe back pain. The implanted device consisted of two longitudinal rods connected to the vertebrae by 22 screws, with two transverse bars for stabilization. Delayed healing of the covering skin was noted over one of the transverse bars; thus, it was subsequently removed to lessen pressure on the skin, which was assumed as the reason for incomplete healing. The local wound included a putrid cyst in the mid spinal area with a periodically opening fistula (Fig. 11.11a). Despite removal of the bar, the cyst had never healed, and every 2–3 weeks, the fistula reopened with putrid discharge. Regardless of the problem, the patient delayed device removal for more than a year, citing the fear of a relapse of his back pain. As the pus was sterile on several occasions, a hypothesis of allergic reaction to the stabilizing device was put forward, and the patient was referred for assessment of the possible role of metal allergy in his problem. The device was made of an alloy-containing niobium (Nb), aluminium (Al), iron (Fe) and

tantalum (Ta). The patient was patch tested to the entire metal series (Chemotechnique). As two metals (Nb and Ta) of the device were not available commercially for testing at that time, test preparations of niobium chloride 2% pet. and tantalum chloride 1% pet. were custom-made and checked in five volunteers (staff members) with negative results. The patient reacted to both niobium from day 2 (Fig. 11.11b) and tantalum from day 3 (Fig. 11.11c), in both cases ICDRG: + and CODEX: C. During patch testing, the putrid discharge from the fistula reappeared, as seen in Fig. 11.11b.

11.3.8 Patient 8: Dental Implant Intolerance

A 55-year-old patient self-reported long-standing recurrences of metal and cosmetic allergy. She had a history of severe intolerance reaction after the fitting of a dental crown: the next day after the procedure, she developed dyspnoea and nausea with recurrent vomiting. She had to be hospitalized, and oral corticosteroids were required to control the symptoms. Two weeks later, the tooth with the newly fit crown was removed, and the patient became symptom-free within a couple of days. Subsequent attempts at mounting dental crowns made of various alloys all caused problems described by her dentists as inflammatory periodontitis, accompanied with periodic fever, throat swelling and erythema with oedema accompanied by a burning sensation of the hands and neck. The patient stated that 'every metal in the mouth caused swelling, nausea and also other problems'. Because of the repeated tooth extractions following crown intolerance, tooth implants were advised. The patient had an array of allergy consultations. She was tested to a sample of the alloy used for the crowns as well as samples of seven various acrylate-based filling materials provided by the dentist, with 'an early reaction after 24 h' to potassium dichromate 0.5% pet. and a 'late reaction after 48 h' to the crown's alloy sample supplied by her dentist described only as a 'Ni-Cr crown'. The readings were performed only after 1 and 2 days. On the basis of the results, the patient was instructed that her problems were caused by chromium which she ought to avoid, and no other contraindications for dental restoration were given. Subsequently, she received three dental implants (Osstem Germany; metals in the alloy: Al, V, Fe, Y, Ti). Within a few days, she developed the same array of symptoms as described above and required steroids to control the symptoms. Following this, the patient was patch tested to the European Baseline Series with negative results to all haptens, including Co, Cr and Ni; she could not recall if the steroids were withdrawn before the tests. At this point, the author had the opportunity to assess the patient. The diagnostic work-up included patch testing to a metal series and dental material series (Chemotechnique), which revealed allergy to cobalt (II) chloride 1% pet. (C-017A, ICDRG: ++, CODEX: C), gold sodium thiosulphate 0.5% pet. (G-005A, ICDRG: ++, CODEX: C—she had reported episodes of eczema underneath her wedding ring that forced her to stop wearing the jewellery), as well as clearly irritant reactions to zinc chloride 1% pet. (Z-007, ICDRG: IR, CODEX: -) and potassium dichromate 0.5% pet. (P-014A, ICDRG: IR, CODEX: -), which might possibly have corresponded with the 'early reaction' to Cr described by a previous allergist. There was also a positive reaction to iron (III) chloride 2% pet. (I-016, ICDRG: ++), which was difficult to assess with regard to clinical relevance. As there was no literature on iron allergy except for contact allergy to iron oxide-based cosmetic pigments and immediate reactions to intravenous iron, the relevance of iron in the patient's implants seemed impossible to credibly assess at this stage (CODEX: D). The only metal of the implant alloy not tested yet was yttrium, which would provoke suspicion as a transition metal; however, yttrium was not commercially available for testing. Therefore, a test preparation of yttrium chloride 2% pet. was produced in our laboratory. Five volunteers (staff members) did not show any reaction to the preparation (except slight erythema in one), while the patient tested positive, thus confirming her hypersensitivity to yttrium (ICDRG: +, CODEX: C). Based on this finding, the decision to remove the implants was made,

which resulted in a rapid resolution of the patient's symptoms. Subsequently, titanium implants were offered to her as the best option available for her dental restoration. The sole metal components in the alloy were Ti (99.66%) and Fe (0.03%). On previous patch tests, she did not react to titanium; thus, the proposed implants seemed a reasonable option. However, given the ++ patch test reaction to iron chloride and her long history of metal intolerance, the recommendation was made to initially fit just one implant in her jaw and wait for a month or two for any possible reactions to emerge. The oral surgeon, however, instead fitted altogether six Ti-Fe implants in one session. The typical symptoms recurred within 10 days, eventually leading to a second implant removal procedure shortly thereafter. This reaction demonstrated that iron allergy was, in fact, also clinically relevant in this patient, changing the final CODEX score into C. The patient received a metal-free, methacrylate-based, removable dental prosthesis, which she has tolerated. In Table 11.4, she is among the six patients with patch test reactions to iron assessed as relevant. In all remaining patients, the relevance could be tracked back to iron oxide dyes in cosmetics, rather than to implanted devices.

11.3.9 Patient 9: Allergy to Niobium in Dental Crowns

A 43-year-old office clerk reported a self-suspected intolerance to dental crowns. Approximately half a year after receiving her first dental crowns, she started having skin problems that she described as 'a rash with breaking and oozing of the skin'. A few months later, she also developed hyperhidrosis, 'breaking blisters' and 'bruises that were coming and going all over the body'. She was then patch tested by an allergist and diagnosed with allergy to nickel. As nickel was present in her dental crowns, they were removed, and all her symptoms ceased within a month's time. Subsequently, her dentist told her that she needed another dental crown; thus, she opted for extensive patch testing to metals before selecting the crowns to be used. She was patch tested to a commercial metal series (Chemotechnique), as well as to hafnium (Hf), niobium (Nb), tantalum (Ta) and yttrium (Y), all of which are used in dental alloys. Within 15 min after patch test application, the patient reported an intense burning sensation at the location of niobium chloride 2% pet. (Fig. 11.12a). This custom-made test substance was previously tested in volunteers and three dozens of patients with only one rather mild irritant reaction recorded; thus, acute toxicity could be ruled out. The test substance was immediately removed from the patient's skin surface with a paper towel, and she was given 20 mg of loratadine to prevent possible contact urticaria syndrome. After another 20 min, the pruritus resolved, and erythema became less pronounced; thus, the patch test unit was mounted again on the patient's back after removal of the chamber with niobium chloride, and after 1 hour of further observation, the patient was sent home symptom-free. Two days later, in the area of the terminated test to Nb, a distinct erythematous macule was present with a tallow-coloured, slightly depressed centre (Fig. 11.12b). Over the course of observation, the lesion gradually took on a more necrotic appearance (Fig. 11.12c). The lesion appeared somewhat vasculitic; however, the patient refused a skin biopsy to verify this suspicion. In the following week, she developed bruises that were 'exactly the same kind as 2 years ago' (Fig. 11.12d). Her dentist confirmed that niobium was indeed present in the alloy used for the crowns fitted in the patient 4 years earlier. Overall, allergic vasculitis to niobium was favoured as the cause of this rare clinical picture. The patient also had typical eczematous patch test reactions to nickel sulphate hexahydrate 5% pet. (N-002A, ICDRG: +, CODEX: O), cobalt chloride hexahydrate 1% pet. (C-017A, ICDRG: +, CODEX: O) and gold sodium thiosulphate 0.5% pet. (G-005B, ICDRG: +, CODEX: D) of no apparent relevance to her present problems. This atypical case illustrates the importance of patch testing broadly and remaining open-minded.

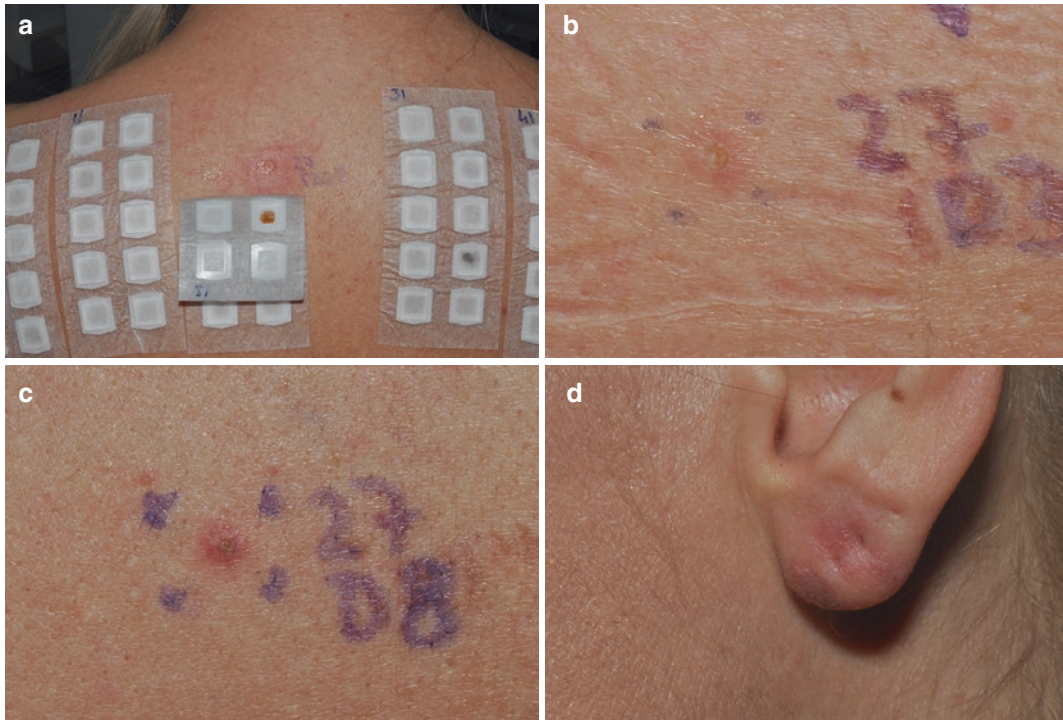

Fig. 11.12 (**a**) Immediate reaction to niobium chloride 2% pet. in Patient 9. (**b**) Erythematous macule with a tallow-coloured, slightly depressed centre in the site of patch test to niobium chloride 2% pet. after 2 days. (**c**) The reaction to niobium with necrotic appearance as seen after 7 days from the start of patch testing. (**d**) A 'bruise' on the patient's earlobe appeared on the seventh day of testing which, according to the patient, was identical with the lesions that appeared when she was first exposed to niobium from her dental crowns

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12 Assessment for Metal Allergy: In Vitro Assays

Thomas Rustemeyer

12.1 Introduction

Various subsets of T-cells are involved in the pathogenesis of allergic contact dermatitis (ACD). The most predominant effector T-cells belong to the CD4+ population [1]. Cytokines, such as interleukin (IL)-4, IL-12, IL-6, or transforming growth factor (TGF)-β, skew the differentiation of T-cells into type 1, type 2, or type 17 effector T-cells, which all secrete distinct patterns of cytokines. Type 1 T-cells produce cytokines such as IL-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, while type 2 T-cells secrete IL-4, IL-5, IL-10, and IL-13. Type 17 helper T-cells produce IL-17, IL-21, and IL-22 [2].

The first described method and current gold standard to diagnose ACD is patch testing. Since its introduction in 1895, the patch test has been the method of choice for ACD diagnosis and is the most used in vivo test [3]. When an individual is suspected to suffer from ACD, the patient is re-exposed to the suspected allergen by patch testing to confirm the diagnosis. However, this method has its limitations, such as false-positive (irritant) reactions [4], interobserver variability [5], poor reproducibility [6, 7], and site-to-site variability [8]. Moreover, patch testing can cause or exacerbate sensitization, which may worsen a person's symptoms [9]. Also, simultaneous use of immunosuppressants or UV-light exposure lowers test sensitivity [10].

Considering these limitations, alternative methods to diagnose ACD have been explored. Lymphocyte proliferation tests (LPT) were introduced in the 1970s and have been used to establish the ability of T-cells to proliferate in response to allergens in vitro [11]. In this assay, primary peripheral blood mononuclear cells (PBMCs) are isolated from blood and cultivated with the suspected allergen for 5–7 days [12]. Whole-blood samples are not used in LPT, as whole blood is a heterogeneous mixture containing many other components besides mononuclear cells that could influence the outcome of the assay. If memory allergen-specific T-cells are present in PBMC samples, they will be activated by the suspected allergen. Activation of memory allergen-specific T-cells can lead to cell proliferation, transformation into lymphoblasts, and allergen-specific cytokine secretion. Proliferation of the cells can be measured by different methods, most frequently by measuring the uptake of radiolabeled ^{3}H–thymidine (3H–TdR) into newly synthesized DNA [11]. Measuring specific cytokine secretion by ELISA or evaluating T-cell activation by flow cytometry is used as well [13]. Proliferation can be compared with lymphocytes incubated in the absence of the suspected allergen and is expressed as the stimulation index (SI). Important to keep in

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mind is that SI values are antigen-specific and have to be evaluated separately for each metal antigen [14]. In general, a SI higher than 3 indicates a positive response, while a SI of 2–3 is considered a weakly positive response [15]. Later, LPT was supplemented with the analysis of cytokine production, which is known as the lymphocyte transformation test (LTT). As compared to patch testing, LPT and LTT cannot sensitize a person as can an in vitro assay.

On the basis of the available literature, this overview aims to describe the usefulness and validity of LTT for the routine diagnosis of metal allergy. In particular, studies are discussed that describe the clinical effectiveness, sensitivity, specificity, reproducibility, and cost-effectiveness of in vitro assays. Finally, the results are discussed and approaches for future research are proposed.

12.2 Memory Lymphocyte Immuno-Stimulation Assay

The Memory Lymphocyte Immuno-Stimulation Assay (MELISA) is a modification of the classic LTT and is suggested to be a validated method for the diagnosis of metal allergy [16]. MELISA was first described in 1994 by Stejskal et al. and is commercially available. The test procedure is highly comparable with LTT. However, there are four differences in MELISA compared with the conventional LTT as stated by the MELISA Medica Foundation (www.melisa.org). Firstly, MELISA uses a higher number of lymphocytes per test. Secondly, the metal concentrations used in MELISA are fixed and thus consist of non-mitogenic and nontoxic metals [17]. Thirdly, monocytes are partially depleted in MELISA, which restores the lymphocyte-monocyte balance to the level that is found in the blood. Lastly, besides the determination of lymphocyte proliferation by radio labeled 3H-TdR, there is a morphological examination of lymphocytes.

Stejskal et al. [18], developers of MELISA, published a study that described the application of MELISA for the first time, in more than 3000 individuals with symptoms of chronic fatigue or people who showed abnormalities in the mouth due to dental amalgam fillings. After the elimination of amalgam fillings or other metals, metal allergy was tested again. The authors showed that there was a decrease of complaints and that positive MELISA reactions decreased as well. However, there was no information provided on the number of control individuals or individual test results. Therefore, no specificity or sensitivity could be calculated based on the results.

The MELISA test was validated in 2003 by Valentine-Thon and Schiwara. In this study, blood from 250 patients with clinical symptoms of type IV hypersensitivity to metal were tested with MELISA against up to 20 metals in 2–3 concentrations. Based on the results, the authors concluded that MELISA is reproducible (94%), sensitive, specific, and reliable for detecting metal allergy in susceptible patients.

12.3 Clinical Effectiveness of LTT and MELISA

After LPT was introduced in 1970 as a method to diagnose metal allergy, many other studies followed describing LTT as a method for testing metal sensitivity in various clinical settings [19, 20]. However, articles published later showed the clinical effectiveness of LTT compared to classic patch testing.

Thomas et al. [21] published a case study which described the diagnosis of titanium allergy using LTT. Formerly, titanium was not considered to provoke allergic reactions, due to its biocompatibility and a history of patch testing which showed no allergic reaction [22]. However, the patient's lymphocytes showed proliferation in vitro upon titanium exposure. After the removal of titanium material, the patient tested negative for titanium allergy with LTT, which demonstrates that titanium-specific memory T-cells are not long-lived. Moreover, Muller and Valentine-Thon [23] showed that titanium allergy was present in 21 out of 56 patients (37.5%) tested for titanium allergy using MELISA, thereby providing additional evidence that titanium can induce hypersensitivity in a group of chronically exposed individuals, which could not

be demonstrated using patch testing as a method of diagnosis. Furthermore, Lindemann et al. [24] demonstrated that a positive LTT outcome was predictive of chromium allergy. They suggested that a cellular in vitro response can discriminate between sensitized individuals with allergy and sensitized individuals without the clinical manifestation of allergy. A patch test is of limited clinical significance, because the test is not positive if an individual is sensitized but not allergic with clinical features. Moreover, they concluded that the diagnosis of chromium allergy should fulfill three criteria: verification of sensitization (a positive patch test), a positive LTT result, and previous exposure to chromium.

The clinical effectiveness of in vitro assays for the diagnosis of metal allergy in patients with total joint arthroplasties is described by various studies as well [25]. Hallab et al. [26] described the lymphocyte reactivity to implant metals chromium, cobalt, nickel, and titanium in patients with and without total hip arthroplasties (THA) using LTT and the measurement of cytokine release. Participants were divided into three groups: controls, subjects with osteoarthritis with and without a history of metal allergy, and total hip arthroplasty patients with or without osteolysis. The study showed that THA subjects demonstrated a stronger lymphocyte response to chromium and cobalt compared to healthy controls and osteoarthritis patients. It was concluded that the incidence and level of lymphocyte reactivity is elevated in THA patients, which suggests an involvement in the pathogenesis of poor implant performance.

12.4 Reproducibility

Reproducibility is an important aspect in order to verify a diagnostic test. Valentine-Thon et al. [27], developer of MELISA, tested its reproducibility. They performed 391 single metal tests in 63 individuals in parallel to assess the reproducibility of the test. They concluded that the reproducibility was 94.9%, with most of the conflicting results in the low-positive test group. Moreover, the same authors demonstrated in a different article that the reproducibility of MELISA used for the diagnosis of metal sensitivity was 94% with a stimulation index cutoff higher than three or 99% using a cutoff higher than 5 [16]. As of now, no independent studies have been published that have addressed the reproducibility of the MELISA assay for various metal allergens.

Gollhausen et al. [6] established the reproducibility of patch testing. A patch test series of 39 substances was tested sequentially in 41 patients and simultaneously in 35 patients. They found that of all positive reactions, 40% were nonreproducible at sequential testing, and 43.8% were nonreproducible at simultaneous testing. Weak positive reactions were more often nonreproducible than strong positive reactions. No studies have been published to date that establish the reproducibility of the conventional LTT when used for the diagnosis of metal allergy.

12.5 Sensitivity and Specificity

In order to assess the diagnostic capability of LTT, it is important to establish the sensitivity and specificity of the assay. There are few recent articles published that validate the use of LTT or MELISA for the diagnosis of metal allergy. In 1997, Nyfeler and Pichler [28] established the sensitivity and specificity of LTT when used for the diagnosis of drug allergies. They found a sensitivity of 78% and a specificity of 85%. They repeated the experiment using patch testing as the method of choice, where they found a lower sensitivity (64%), while the specificity was the same (85%). Therefore, the authors concluded that LTT is a useful diagnostic test in drug allergies.

However, some studies have been conducted that evaluate the sensitivity and specificity of LTT when used for the diagnosis of metal allergies. Cederbrant et al. [29] focused on establishing the sensitivity and specificity of conventional LTT compared to MELISA for the diagnosis of metal allergies to gold, palladium, and nickel. Sensitivity and specificity of the two assays was calculated using patch testing as a reference method. The authors concluded that there were no significant differences compared to traditional patch testing, and sensitivity varied between

55 and 95% with the specificity varying between 17 and 79%. Due to the low specificity of the two assays, they recommended not to use in vitro assays as diagnostic tests, since a large number of false-positives would be obtained. Therefore, they advised to use patch testing as the method of choice.

In 1999, Cederbrant et al. published a different study in which mercury allergy was tested to assess the validity of MELISA. Mercuric chloride in low concentrations (0.5 μg/L) was used as an allergen. High concentrations of mercuric chloride result in nonspecific lymphocyte proliferation and therefore in false-positive reactions [30]. It was concluded that the proliferation of lymphocytes in vitro in the presence of mercuric chloride cannot be used as an objective marker for mercury allergy in individuals with dental amalgam fillings. A high frequency of false-positive reactions was observed, due to a low sensitivity. These results are in agreement with those obtained by Martins et al. [31]. They determined the appropriate salt, concentration, and period of incubation for the chromium LTT and calculated the specificity and sensitivity of the assay. The best specificity and sensitivity results were achieved with an incubation period of 6 days with concentrations varying between 7.5×10^{-4} and 5×10^{-3} mol/L chromium chloride. Within this range, the specificity was 95% with a sensitivity of 65%. They concluded that further research was needed to improve the testing sensitivity.

For comparison, the sensitivity of patch tests has been estimated to be around 75% for type IV hypersensitivity reactions [32]. It is generally presumed that the sensitivity and specificity of patch testing is between 70% and 80%, with a lower sensitivity compared to specificity [33, 34].

12.6 Lymphocyte Transformation Tests and Cytokines

Various studies described the supplementation of cytokines to improve LTT by stimulating antigen presentation, proliferation, expression of costimulatory and adhesion molecules, and mediator release of specifically activated T-cells in order to diagnose nickel allergy. McKimm-Breschkin et al. [35] were the first to describe the production of allergen-specific IFN-γ after lymphocyte stimulation. After this publication, many articles followed which described the role of antigen-specific cytokine production.

Previously, T lymphocytes involved in contact nickel allergy were regarded as type 1 helper T-cells. Cavani et al. [36] described that nickel-allergic individuals primarily showed Th1-type-specific cytokines, while nonallergic subjects showed T-regulatory 1 (Tr1)-type cytokines with high IL-10 production. However, studies published in recent years have attributed a role for Th2-type and Th0-type T-cells in contact allergy as well [37].

Rustemeyer et al. [34] used cytokines (IL-4, IL-7, and IL-12) to improve lymphocyte proliferation assays for the diagnosis of nickel allergy in a study including 156 patients. Type 1 (IFN-γ release) and type 2 effector T-cell function (IL-4, IL-5, and IL-13 release) was monitored in combination with regulatory T-cell function (IL-10 and TGF-β secretion). They found that both T-cell proliferation and cytokine secretion, in particular IL-5 release using IL-4- or IL-7-supplemented medium, improved in vitro diagnostics of nickel contact sensitization. Diagnosing nickel allergy with the proliferation test supplemented with cytokines showed an accuracy of 82%. In contrast, patch testing showed an accuracy of 76%, and proliferation tests without cytokines showed an accuracy of 68%. Moreover, nickel-induced IL-10 secretion might help to identify nickel-tolerized persons. The importance of Th2-type T-cell responses and IL-4 as a nickel allergy marker was also demonstrated by Minang et al. [37]. The study aimed to define Th1-type, Th2-type, and regulatory cytokine responses to nickel in PBMC samples from subjects with varying patch test results to nickel with enzyme-linked immunospot assay (ELISpot) and enzyme-linked immunosorbent assay (ELISA). They found that IL-4 and IL-13 can serve as reliable markers for nickel allergy, which indicates a Th2-type cytokine profile.

Furthermore, Cederbrant et al. [38] aimed to analyze whether the secretion of cytokines, IL-10 and IL-17 in particular, would be more useful for discriminating between nickel allergic and nonallergic subjects. PBMC cultures were assessed for cell proliferation by 3H–TdR incorporation and for the production of IFN-γ, IL-4, IL-10, and IL-17 in the supernatant with ELISA. They found that the identification of IL-10 secretion in primary PBMC cultures is a promising in vitro method for the discrimination of nickel allergy as compared to lymphocyte proliferation.

Spiewak et al. [39] aimed to strengthen the in vitro assay by skewing lymphocytes toward a type 1 (IFN-γ secreting) or type 2 (IL-5 and IL-13 secreting) phenotype. The cytokine cocktails that were used to skew the phenotypes consisted of Il-7 and IL-12 or IL-4, respectively. Cell responses to nickel were measured with ELISpot, ELISA, and LPT. They found significant differences between nickel-allergic contact subjects and controls for type 2 cytokines IL-5 and IL-13, with an increase of allergen-specific cytokine secretion when the cytokine cocktails were added. They concluded that the best way for the diagnosis of nickel allergy was LPT with type 2 cytokine skewing. This finding corroborates the previously mentioned findings of Rustemeyer et al. [34] and Minang et al. [37].

However, few studies have described the cytokine profile induced in vitro by metal sensitizers other than nickel. A study published by Minang et al. [40] looked into the cytokine profile induced by nickel, cobalt, chromium, palladium, and gold in PBMC from subjects with patch test reactivity to these respective metals. Collected PBMC samples were stimulated in vitro with corresponding metal components. The authors described a mixed Th1- and Th2- type cytokine profile after challenge with all metals tested. Lindemann et al. [24] found a corresponding result. The group demonstrated that sensitized subjects with and without metal allergy did not differ significantly in cytokine profile when challenged with chromium compounds.

12.7 Discussion

Currently, patch testing is regarded as a useful and reliable method for the diagnosis of ACD and is widely used in the clinic. However, patch tests have various limitations, such as the possibility of provoking sensitization and interobserver variation. Therefore, an objective, simple and safe diagnostic method to identify contact allergy would be of considerable use. LTT has been used as an in vitro assay for the detection of contact allergy and is currently mainly used in an experimental setting. The present literature review aimed to explore the validity of LTT as a routine diagnostic method for allergic contact dermatitis. This chapter included studies that described the specificity, sensitivity, reproducibility, and clinical results of diagnostic in vitro assays for metal allergy.

The use of in vitro assays for metal allergy diagnosis has various advantages compared to conventional patch testing. As discussed previously, patch testing has a wide variety of limitations, including the possible induction of sensitization. As an in vitro test, LTT is not able to sensitize a person, which is considered a major advantage. Another advantage of LTT compared to patch testing as a diagnostic method is the possibility of LTT to identify more metal allergens which were not detected previously, as demonstrated with titanium allergy. Formerly, it was thought that titanium could not provoke allergic reactions due to its biocompatibility. However, diagnosing this allergy with LTT did show lymphocyte proliferation, which indicates an allergic reaction, while there was no positive result using patch testing. Nevertheless, titanium allergy remains a rare condition [21]. Moreover, in contrast to patch testing, it was established that LTT appears to be the method that is most predictive of chromium allergy. Furthermore, LTT provides objective and quantitative results, while the outcome of patch testing is subjective and may involve interobserver variability, which leads to less reliable results and possible misdiagnosis. When using patch testing, site-to-site variability can occur that might influence the outcome of the

test as well. By using a patient's PBMC in in vitro assays, site-to-site variability is impossible.

Several limitations must be considered when evaluating the validity of LTT for routine clinical diagnosis. First of all, PBMC have to be incubated with the suspected allergen for 5–7 days, which is time-consuming. Diagnosing metal allergies with patch testing requires less time, namely, 2–4 days. Using LTT as a method of choice for the diagnosis of metal allergy will thus lead to prolonged diagnosis. Secondly, sufficient laboratory equipment and trained staff are required for the proper execution of LTT. This also applies to patch testing; however, less expensive laboratory equipment is needed for this assay. Thirdly, it has been established that incubation with high concentrations of suspected allergens can result in nonspecific lymphocyte proliferation and can result in false-positive reactions [30]. When the metal concentration used during incubation is too low, it could lead to false-negative reactions. Therefore, it is important to standardize the concentration and incubation time for each allergen when using LTT for the diagnosis of metal allergy. Currently, no standardization has been carried out. Another disadvantage of LTT as a diagnostic method is the decrease in proliferative response in lymphocytes, which usually declines within 4–8 weeks after withdrawal of the metal allergen [36]. This decrease is probably due to the homing of lymphocytes to lymph nodes, which hinders the detection of lymphocytes in peripheral blood. However, in some cases, specific sensitization can be detected with LTT for several years [1, 41].

Previous studies evaluating the validity of LTT(−MELISA) observed inconsistent results on the sensitivity and specificity of the assay. Valentine-Thon and Schiwara [16] concluded that the MELISA assay is a sensitive and specific test to establish metal allergy. However, there are conflicting results regarding the sensitivity and specificity of the MELISA test. Cederbrant et al. [29] established the sensitivity and specificity of MELISA and conventional LTT. They concluded that both MELISA and the conventional LTT were not sensitive enough, with many occurrences of false-positive results. This finding was shared by Martins et al. [31], who stated that the sensitivity of LPT is too low to reliably establish chromium allergy. The sensitivity and specificity are dependent on the cutoff values above which the test is regarded as positive. In the articles mentioned previously, the cutoff value for MELISA was SI $\geq$ 3; the cutoff value for LTT was SI > 3, while the cutoff value for LPT was SI $\geq$ 2. This illustrates that the cutoff values used in the articles were not all equal, which could lead to the inconsistent results, although the cutoff values do not vary greatly. In general, particularly the specificity of LTT is somewhat higher compared to classic patch testing, although this difference is not consistent in all studies. Due to this inconsistency, it is not possible to reliably establish the sensitivity and specificity of the test. Moreover, only a few articles were found on the sensitivity and specificity. Therefore, it is advised to further analyze the sensitivity and specificity of in vitro tests using a fixed cutoff value for the stimulation index.

Besides sensitivity and specificity, it is important to be aware of the reproducibility of diagnostic tests in order to establish their usefulness for routine diagnosis. Only one article was found regarding the reproducibility of MELISA. This study was published by members of the MELISA group, Valentine-Thon, and Schiwara [16], which concluded that the reproducibility was 94% or 99% using a SI cutoff value of 3 and 5, respectively. This finding implies that the reproducibility is high, and this assay provides consistent results. However, due to the limited number of resources, it is hard to establish the true reproducibility of MELISA. Moreover, no publications were found that demonstrated the reproducibility of conventional LTT or LPT. Therefore, further studies assessing the reproducibility of in vitro assays are needed.

The usefulness of the MELISA test compared to a conventional LTT is questionable. In 1999, MELISA was used experimentally for the first time by Stejskal et al., who also developed the test. It was concluded that MELISA was a useful assay to diagnose metal allergy. However, in this publication, there is no information about control

individuals, and the authors had a financial interest in the success of MELISA. Stejskal et al. published more articles in the following years where they established the usefulness of MELISA. In 2003, the test was validated by Valentine-Thon and Schiwara. They concluded that MELISA is a reproducible, sensitive, specific, and reliable test for detecting metal sensitivity in metal-sensitive patients. This publication seems to come from an independent source. However, this study is published by a commercial MELISA laboratory established in Europe [42]. Therefore, it has to be taken into account that these findings may not be reliable as they do not come from an independent source. In addition, Cederbrant et al. published articles in 1997 and 1999 in which they recommend not to use MELISA for the diagnosis of contact allergy. Prior to these publications, Cederbrant was one of the researchers that published the first article that described MELISA in 1994. No other independent studies have been published that evaluate the validity of MELISA. Therefore, independent research is needed to establish the validity of LTT-MELISA.

Some studies have focused on improving the in vitro test protocol for the detection of allergen-specific lymphocyte responses with the supplementation of cytokines during incubation with suspected allergens. Various studies found that protocol modifications improved detection of allergen-specific lymphocyte responses in vitro. However, all of these studies solely investigated the lymphocyte response to nickel and did not include other metal allergens. Other studies tried to establish the importance of Th1- or Th2-type cytokine responses during metal-specific lymphocyte reactions [43]. Results provided by these studies showed that cytokine responses are dependent on the metal allergen that is used in the in vitro assay. Incubation with nickel showed a Th2-type cytokine profile, while incubation with other metals, such as chromium, showed mixed cytokine profiles. This illustrates that the immune system secretes different cytokines when stimulated with various allergens and that a cytokine profile might be predictive for one but not for other allergens.

Further research should be undertaken to establish the usefulness of LTT as a method for routine metal allergy screening [44, 45]. There are several recommendations for further research. Until now, no studies have been published regarding the cost-effectiveness of LTT which would be of great help in establishing the usefulness of the in vitro assay for regular metal allergy diagnosis. It is reasonable to infer that patch testing costs less than LTT; however, no research has been carried out to confirm this. Therefore, it was not possible to evaluate the cost-effectiveness of LTT for routine metal allergy screening. Moreover, research could be carried out concerning the cost-effectiveness of the lymphocyte transformation assay compared to the classic patch test. Studies evaluating the sensitivity and specificity of in vitro tests have showed conflicting results. It is advised to further investigate this topic. In the past, it has been proposed that combinations of 2 or 3 different in vitro methods would have the ability to overcome the poor sensitivity and/or specificity of the assays [46]. However, this approach has not been used in the clinic. More research could be conducted to verify this finding. By combining two or three different in vitro methods, it is possible that the cost-effectiveness of metal allergy diagnosis worsens. In addition, there are no published studies that describe the reproducibility of LTT, and just one article has been published regarding the reproducibility of MELISA, by members of the MELISA group with possible competing interests.

Based on the results discussed in this literature review, it is recommended not to use LTT as a method for routine metal ACD screening. Currently, in vitro tests provide an alternative to patch testing and may serve as an additional method in diagnosing ACD. In some experimental settings, it is feasible to use in vitro assays. Various studies have showed that LTT is a useful method for the establishment of metal contact dermatitis in subjects with total joint arthroplasties. However, none of the in vitro assays for metal contact dermatitis are easy and accurate with sufficient sensitivity and specificity as would be required for use in routine diagnosis. Due to the poor sensitivity and lack of

information concerning the reproducibility and cost-effectiveness of the assays, further studies would be helpful in the development of an in vitro diagnostic assay or an alternative diagnostic method for metal allergy.

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Part III

Common Sources of Metal Exposure

Metals in Everyday Life

13

Carsten R. Hamann and Dathan Hamann

13.1 Introduction

Metal allergens are among the most common causes of allergic contact dermatitis (ACD), and modern humans are exposed to these allergens frequently in daily life. Nickel, cobalt, and chromium are often found in everyday consumer objects, such as jewelry, clothing, leather, technological devices, household items, and other daily-use objects [1]. Gold, palladium, mercury, copper, aluminum, titanium, iron, platinum, tin, zinc are also occasionally found in these items. Metal ACD due to daily-use objects is exceedingly common. Nickel is by far the most common cause of ACD and is ubiquitous in consumer goods [2, 3].

There are two general ways to report metal exposure via daily-use objects. First, there are exposure studies, or studies that survey a large sample of a certain type of product or item and assess metal content or release. These types of studies have been performed since the late 1970s and early 1980s when clinicians used new synthetic sweat methods to detect nickel ion release from jewelry and clothing snaps [4, 5]. Exposure studies do a good job describing the exposure patterns individuals may have when they use a certain type of product in a certain setting. However, it is not necessarily easy to apply these studies to clinical practice, as they can be very setting specific, e.g. studies reporting on metal release from jewelry from Asia may not be applicable to a clinical practice in Europe. Additionally, if they are not guided by clinical data they can be clinically irrelevant, e.g. an exposure study of metal release from computer components is not clinically relevant unless, clinically, individuals are having adverse reactions to computer components.

Secondly, one can use clinical reports to describe metal content in daily-use objects. Case reports, case series, and clinical vignettes provide important information regarding the clinical consequences of metal exposure via everyday devices and should be used as a basis for guiding exposure studies. A good example of this is a case report of nickel ACD from a laptop computer, prompting multiple exposure studies evaluating laptops and other technological devices for allergenic metal ion release [6, 7]. Like exposure studies, however, case reports and other clinical reports again are not necessarily generalizable given their case-specific nature.

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13.2 Methods for Measuring Metal Content and Release

This topic is discussed in depth in other chapters (see Chap. 6). Briefly, there are two primary ways to evaluate metals in daily-use objects: there are methods that measure metal content and methods that measure metal release. Frustratingly, metal content does not always predict metal ion release or bioavailability [8]—for example, many nickel-containing stainless steel alloys do not release nickel in sufficient doses to elicit ACD in nickel-sensitized individuals. For this reason, measuring metal release is generally more clinically useful. Metal release is often qualitatively assessed by spot tests, such as the dimethylglyoxime (DMG) spot test for nickel release, and the newer cobalt and chromium spot tests. These are convenient, quick, economical, non-destructive screening tests which identify metal ion release from most metallic, non-porous surfaces [9–11]. These techniques are limited, however, both in scope—there are no release tests for other common metal allergens, such as copper and palladium—and in the range of items they can test—they cannot be used on non-metallic items, e.g. make-up, emollients/moisturizers, leather. Content tests, such as X-ray fluorescence spectroscopy and atomic absorption, can provide information on all metal elements and can be used to evaluate non-metallic items but can be impractical, expensive, and in some cases damaging to the item in question [8, 12, 13].

13.3 Metals in Jewelry

Worldwide, jewelry is the most common source of daily metal allergen exposure. In order of relative worldwide frequency, the most common metals found in jewelry are copper, iron, zinc, nickel, silver, chromium, tin, manganese, lead, and cobalt [8]. Among patients with metal allergy who develop dermatitis from jewelry, there is significant variation in severity of symptoms, ranging from minor irritation to severe dermatitis with id reaction or even systemic contact dermatitis. Metal exposure via jewelry is significant not only because of the ubiquitous use of metallic jewelry, but also because the friction, sweat, and occlusion that occur with jewelry use can facilitate release of metal ions from otherwise non-ion releasing alloys—a concept identified in even the earliest jewelry ACD case series [14, 15].

13.3.1 Nickel in Jewelry

Nickel is the most common cause of ACD from jewelry. Modern jewelry from Europe, North America, and Asia frequently releases nickel sufficient to cause ACD [8, 16–19]. Modern case reports of nickel dermatitis from jewelry date back to the early twentieth century—for example, one series of cases described dermatitis caused by nickel in bracelets, a wrist watch, and a wrist watch band [20]. Numerous case reports and exposure studies have detailed nickel ACD or nickel release from jewelry items including navel and genital rings [21–23], hair bands [24], and hair clips [25] (see Table 13.1). Unsurprisingly, nickel contact allergy has been shown to correlate with wrist, finger and ear dermatitis, common locations jewelry is worn (see Figs. 13.1 and 13.2) [26].

In contrast to cobalt and chromium, jewelry is the primary sensitizing exposure for nickel allergy. Worldwide prevalences of nickel allergy are increased in women compared to men due to nickel exposure in earrings and jewelry. For example, among North American dermatitis patients, 23% of female patients had positive nickel patch testing compared to only 7% of male patients [27]. Similarly, men with pierced ears have higher rates of positive nickel patch tests compared to men without ear piercings [28]. Ear piercing, body piercing, number of piercings, and young age at piercing are all significant risk factors for nickel allergy [27, 29–31].

Nickel is often used in jewelry alloys and platings due to its low cost, attractive white shiny appearance, and resistance to corrosion. While several studies found that inexpensive jewelry is more likely to release nickel [18, 19, 32, 33], another study found no association between price and likelihood of nickel release [34]. Expensive

Table 13.1 Exposure studies evaluating jewelry for metal ion release

Sources—selection criteria	Country	Metal	Method of detection—number positive (%)	Citation
Combination of unused and dermatitis-causing earrings	Sweden	Nickel	Synthetic sweat AAS[a] method—28/28 (100%) released 0.005–442 mcg/item/week	Fischer et al. [5]
Earring, watches bracelets, of the 21 total pieces 3 were and 18 were not tolerated by nickel-sensitive subjects	France	Nickel	DMG—16/21 (76%)	Cavelier et al. [76]
Earring components	Finland	Nickel	DMG after artificial sweat incubation—9/66 (14%) 11–25/66 (17–38%) with more complex methods at levels >0.5 mcg/cm^2 per week	Pönkä and Ekman [77]
Earrings, necklaces, watches, hair clasps, bracelets, and spectacle frames	Sweden	Nickel	DMG—69/401 (17%)	Lidén and Johnsson [78]
Earring posts intended for piercing	Sweden	Nickel	EN 1810[b]—9/15 (60%)	Lidén and Johnsson [78]
Earrings, necklaces, watches, hair clasps, bracelets, spectacle frames, and rings	Sweden	Nickel	DMG—49/510 (10%)	Lidén and Norberg [79]
Earring posts intended for piercing	Sweden	Nickel	EN 1810[b]—3/18 (17%)	Lidén and Norberg [79]
"Nickel-free" inexpensive earrings	Italy	Nickel, cobalt, chromium	EN 1811[c]—5/10 (50%), SF-ICP-MS[d] and artificial sweat co release—3/30 (30%), SF-ICP-MS[d] and artificial sweat Cr release—3/30 (30%)	Bocca et al. [38]
Earrings	South Korea	Nickel	ICP-AES[e] and synthetic sweat release—3/9 (33%)	Kim et al. [80]
Earrings	United States	Nickel	DMG—85/277 (31%)	Thyssen et al. [34]
Earrings, bracelets, necklaces, rings, hair clasps. "Nickel-free" items intentionally avoided	Denmark	Nickel, cobalt	DMG—78/354 (22%), cobalt spot test—4/354 (1.1%)	Thyssen et al. [18, 21]
Earrings, necklaces, watches, hair clasps and bracelets	Sweden	Nickel	DMG—25/305 (8.2%)	Biesterbos et al. [33]
Earrings	China and Thailand	Nickel	DMG—170/557 (30%)	Hamann et al. [17]
Earrings, spectacle frames, hair clasps, watches and necklaces with possible clinical relevance to nickel-allergic patients	Denmark	Nickel	DMG—22/61 (36%)	Thyssen et al. [81]
Wide range of jewelry items including earrings, necklaces, watches, rings, and bracelets	The Netherlands	Nickel	DMG—27/238 (11%)	Biesterbos et al. [32]
Earrings	China and Thailand	Cobalt	Cobalt spot test—4/557 (0.7%)	Hamann et al. [49]
Earrings	Poland and the United Kingdom	Nickel	DMG—69/411 (17%)	Thyssen et al. [19]

(continued)

Table 13.1 (continued)

Sources—selection criteria	Country	Metal	Method of detection—number positive (%)	Citation
Earrings currently being used by 15-year-old schoolchildren	Poland	Nickel	DMG—5/50 (10%)	Krecisz et al. [82]
Bracelets, earrings, hair pins, necklaces, watches, rings (gold and silver jewelry excluded)	South Korea	Nickel, cobalt	DMG—150/374 (40%) cobalt spot test—12/374 (3.2%)	Cheong et al. [16]
Bracelets, earrings, necklaces, rings and watches	Thailand	Nickel, cobalt	DMG—204/523 (39%) cobalt emersion test[f]—198/523 (38%)	Boonchai et al. [52]
Earrings	Denmark	Chromium	Chromium spot test —1/50 (2%)	Bregnbak et al. [83]
Earring components previously analyzed for Ni release by Thyssen et al. [9, 34]	United States	Cobalt	EN 1811[c]—35/96 (36%) (96 components from 73 total earrings)	Hamann et al. [8]

[a]AAS—atomic absorption spectroscopy
[b]EN 1810—an established reference method for establishing nickel content based on atomic absorption spectroscopy [84]
[c]EN 1811—an established reference method for establishing nickel release from items intended to come into prolonged contact with the body, based on a 7-day synthetic sweat bath and analysis with atomic absorption spectroscopy, inductively coupled plasma mass spectrometry or other appropriate technique [85]
[d]SF-ICP-MS—sector field inductively coupled plasma mass spectrometry
[e]ICP-AES—inductively coupled plasma optical emission spectrometry
[f]Cobalt emersion test—emersion of test items in cobalt spot test solution for 5 min

jewelry items and gold alloys—such as white gold, and rhodium-plated gold—may also release nickel [35–37]. Nickel release from jewelry items marketed as "nickel-free," or labelled as stainless steel or sterling silver, has also been reported [38]. Stainless steel frequently contains nickel, but clinically relevant nickel release is uncommon [39].

Historically, eyeglasses and spectacle frames constituted an important source of nickel exposure [40]. In fact, some of the earliest reported cases of non-occupational nickel ACD were from glasses frames [15, 20, 41]. Glasses frame dermatitis was reported in 56% (43/77) of nickel-allergic patients in a large facial dermatitis cohort, many of whom had nickel-releasing frames on DMG testing [42]. Many eyeglasses frames are now made of plastics and other metals. For example, in one case of eyeglasses dermatitis, a known nickel-allergic patient reacted to palladium in nickel-free glasses frames [43]. Nevertheless, exposure studies continue to identify nickel release in large portions of glasses frames [40], and nickel glasses frame ACD is still reported [44].

Simple cases of nickel dermatitis from jewelry or glasses frames are uncommonly referred for patch testing. While jewelry dermatitis classically closely matches the anatomical site of exposure (i.e., neck dermatitis from a nickel-releasing necklace), jewelry must not be overlooked as a cause of distant dermatitis as well, particularly for the face. Transfer of nickel ions in jewelry may also be responsible for ear, eyelid, lip, or facial dermatitis (see Fig. 13.3) [45, 46].

13.3.2 Cobalt in Jewelry

The classic historical example of relevant cobalt allergy is mid-twentieth century women with cobalt and nickel dermatitis due to garter suspenders [47, 48]. It is unclear, however, if cobalt exposure in jewelry or daily-use objects continues to drive cobalt contact allergy in the twenty-first century. For example, while jewelry from Europe, North America, and Asia often contain cobalt [8], cobalt is rarely released [21, 49], and jewelry dermatitis from cobalt is rarely seen in

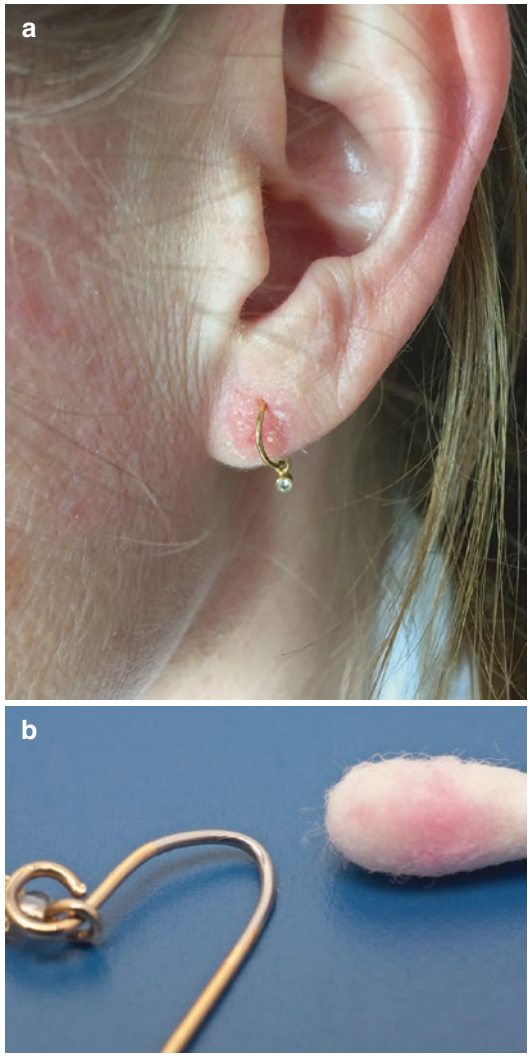

Fig. 13.1 (**a**) Earlobe dermatitis after contact with metal earrings in a known nickel-sensitive individual. (**b**) Positive DMG test from earring post. The gold colored plating had worn away from the portion of the earring post that came in contact with the skin revealing the silver-colored metal below. Only the silver-colored metal released nickel

clinical practice. To our knowledge, there is only one published case of clear jewelry dermatitis to cobalt in the recent literature [50]. It has been demonstrated that jewelry and belts with a dark metallic finish are more likely to release cobalt [21, 51]. Most contemporary exposure studies in Europe and North America aimed at assessing cobalt release from daily-use objects are performed with a cobalt spot test and the majority of these studies find that cobalt release from jewelry is very rare—for example, in the USA and Denmark cobalt release from jewelry is found in ~1% or less [21, 49]. There are several studies of cobalt release from jewelry in Asia: one study from China and Thailand demonstrated very rare release of cobalt from jewelry while two others from Korea and Thailand found relatively frequent release of cobalt from belts and jewelry [16, 49, 52]. A recent study did evaluate cobalt release from earring components in Europe using the EU 1811 artificial sweat analysis rather than the spot test and found considerable release from at least one component of 44% of tested earrings [53]. Interestingly, cobalt and nickel co-sensitivity is frequently seen in patch tested patients and this has always been explained by co-exposure. It has been clearly demonstrated that ear piercing is associated with nickel allergy, but ear piercing does not appear to be a contemporary risk factor for cobalt allergy [27, 54]. This suggests that cobalt sensitization from earrings is not significant on a population level. Interestingly, in one study cobalt contact allergy was shown to correlate with wrist and finger dermatitis, common sites of jewelry use [26]. Ear dermatitis due to cobalt allergy is not a common clinical problem but dermatologists should be aware that jewelry may be a source of exposure for some cobalt-allergic patients.

13.3.3 Chromium in Jewelry

Chromium is a common component of most stainless steel alloys and is present in jewelry worldwide [8]. Despite jewelry frequently containing chromium, hexavalent chromium release was only found in 1/848 (0.1%) pieces of jewelry by the chromium spot test [11]. Dermatitis from chromium in jewelry is not a common clinical problem; however, occupational dermatitis after handling metallic items has been more frequently reported [55], and recent investigations have demonstrated significant levels of cutaneous chromium deposition after handling chromium-containing metal discs, even with short exposure

Fig. 13.2 Positive DMG test from a nickel-releasing ring

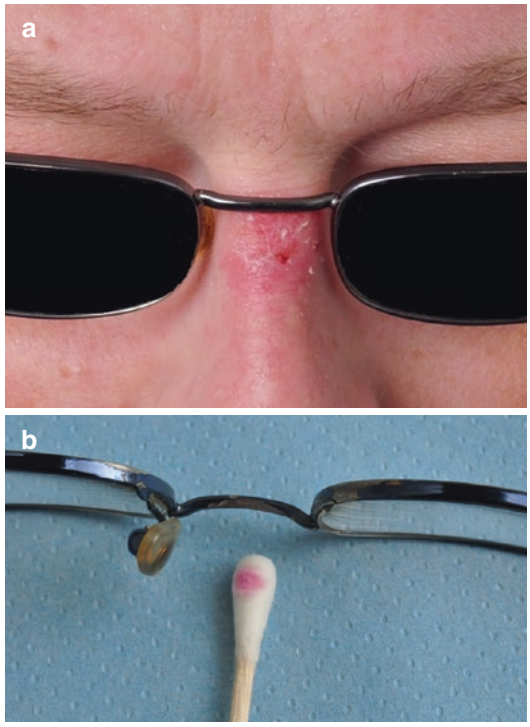

Fig. 13.3 (**a**) Bridge of the nose dermatitis corresponding to resting location of metal eyeglasses (**b**) Positive DMG test from metal eyeglasses

times [56]. Like cobalt, on a population level chromium exposure via jewelry does not seem to be a significant cause of chromium ACD, but may be relevant to individual chromium-allergic patients.

13.3.4 Gold in Jewelry

Gold is a controversial allergen. While positive patch test reactions to gold salts such as gold sodium thiosulfate are common, the relevance of positive gold patch testing is often difficult to ascertain. Though not commonly found in cheap jewelry globally, gold is a precious metal commonly used in the alloys for expensive jewelry [8]. While gold salts are immunologically reactive and were previously used as inflammatory modulators for rheumatologic diseases [57], metallic gold has long been valued for being relatively inert and resistant to corrosion. In one study, gold was not released from gold-containing jewelry when assessed with artificial sweat and atomic absorption analysis and the authors concluded that jewelry was unlikely to provoke dermatitis, even in those with positive gold patch tests [58]. Another study confirmed insignificant release of gold from gold alloy discs in artificial sweat; however, they did find that gold was released when the discs were soaked in more complex mediums containing cysteine or glutathione [59]. Additionally, it was recently reported that gold is released from elemental gold discs and deposited onto the skin when applied under occlusion to the backs of healthy individuals [60]. Metallic gold in dental alloys and vascular stents has been shown to increase serum gold levels and correlates with positive gold patch testing [61].

Due to low relevance and unusual clinical presentations, experts disagree about the utility of patch testing with gold. However, there is some evidence that gold may be an important allergen. For example, nearly half of gold-allergic patients developed dermatitis when they were re-exposed to gold earrings in a blinded study [62]. This provides good evidence that jewelry may be a relevant exposure for gold allergic patients. Interestingly, gold ACD may not develop at the site of cutaneous exposure, as is common with other metal allergens. Rather, jewelry-related gold ACD may manifest only as periorbital or facial dermatitis which may resolve only after several months of avoidance of gold jewelry [63–65]. Gold may also cause persistent and granulomatous reactions both from patch testing and from exposure to jewelry [66, 67]. Gold allergy is more common in women compared to men, which also suggests that jewelry, rather than dental alloys or occupational exposures, may play a primary role in gold sensitization [65].

13.3.5 Palladium in Jewelry

Palladium contact allergy is most commonly associated with oral lichenoid reactions and stomatitis from dental alloys [68]. Palladium and nickel cross-react and true mono-palladium hypersensitivity (in the absence of nickel allergy) is rare [69]. However, there is some evidence that palladium allergy may be underdiagnosed given that the palladium salt historically most commonly used for patch testing, palladium dichloride, may have low sensitivity [70]. Nevertheless, there are reports of palladium ACD from eyeglasses frames [43] and palladium may be found in expensive jewelry. Interestingly, one palladium-sensitive patient with chronic pain and swelling adjacent to a palladium-containing dental implant developed finger dermatitis when challenged with a palladium ring, suggesting that cutaneous palladium exposure elicit produce ACD in strongly sensitized individuals [71]. When palladium allergy is seen after ear piercing, a granulomatous reaction may occur—sometimes called an allergic contact granuloma [72]. In one study of patients with palladium positive patch tests, no skin reactions were observed when they wore palladium-coated earrings for 9 weeks [73].

13.3.6 Presumed Jewelry Allergy and Other Clinical Considerations

Patients may self-diagnose nickel allergy and avoid jewelry and other items which clearly cause dermatitis at the site of cutaneous exposure. In addition, many primary care physicians and dermatologists are aware of nickel allergy and may diagnose and counsel patients who present with characteristic distributions of jewelry dermatitis without recommending patch testing. Suspected jewelry dermatitis is often considered a simple clinical problem. While in some cases patch testing is not required to make the diagnosis of nickel ACD from jewelry, we caution physicians against delaying patch testing if the dermatitis does not resolve promptly after removing the presumed offending source of exposure. Presuming a mono-allergy (i.e. nickel allergy only) in a patient may delay correct diagnosis and increase morbidity for patients with multiple contact allergies. In a study of 449 patients with a self-reported history of jewelry dermatitis, nearly half of all nickel-allergic patients also had a positive patch test reaction to either gold, cobalt, chromium, palladium, or platinum when patch tested to an expanded metal series [74]. As a clinical example, after a positive nickel patch test, a woman was counseled to avoid nickel-releasing jewelry but had continued difficulty with neck dermatitis. She was found to be both nickel and cobalt allergic on repeat patch testing and had a new cobalt-releasing necklace [50].

Furthermore, patients may be erroneously diagnosed in the absence of patch testing—for example, suspicions of titanium allergy are commonly unfounded, may delay orthopedic surgical procedures, and provoke significant patient distress. One woman began to react to her “titanium” eye-glasses and was erroneously given a diagnosis of presumed titanium allergy shortly before an orthopedic procedure. Upon patch test-

ing, the patient was nickel-allergic and the glasses were subsequently found to release nickel, containing very little titanium [75]. Clinicians should not hesitate to perform patch testing for patients with unresolved presumed jewelry dermatitis.

13.4 Copper in Everyday Use Objects

Copper-containing alloys, including bronze, brass, and many others, are very commonly found in jewelry in North America, Europe, and Asia [8]. In addition, it has been demonstrated that earrings with copper content also release copper as assessed by artificial sweat leaching and inductively coupled plasma mass spectrometry [38].

Copper is an infrequent sensitizer, and the clinical relevance of positive patch testing to copper salts is controversial. The allergenicity of copper has been demonstrated by local lymph node assay in animal models [86]. Though not regularly tested, copper allergy has been assessed in patients with 1–5% copper sulfate in petrolatum or 1–2% copper sulfate in aqueous preparations. In large studies, copper patch test positivity is often seen in conjunction with positive patch tests to other metals; for example, in a Swedish study of 1190 dermatitis patients 9/13 (70%) patients with a positive patch test to copper sulfate 2% had a concomitant reaction to either nickel, cobalt, or chromium [87]. Though rare, copper ACD from jewelry has been reported [88]. Copper ACD was reported to cause chronic hand dermatitis in an electrician [88] and recurrent fingertip dermatitis in a child who often played with die-cast model cars containing copper [89]. In addition to jewelry, copper is also found in coins, electronics, dental alloys, and industrial applications. Copper-containing intrauterine devices for long-term reversible contraception are used worldwide. Localized and generalized dermatitis, as well as urticaria, in patients with copper IUDs has been reported, and many cases have resolved with removal of the copper device [90–93]. There is experimental evidence that copper may cross-react with nickel [94] and palladium [95]. Copper is an uncommon cause of ACD to daily-use objects; however, there is good evidence that copper may cause ACD and testing should be undertaken when clinical suspicion is high.

13.5 Metals in Clothing, Textiles, and Leather

Clothing, textiles, and leather are an underappreciated source of metal exposure in everyday life. While much of the historical metal exposure through clothing is likely no longer clinically relevant to today's patch testing clinicians, e.g. nickel dermatitis to corset fasteners, etc. [41], metal exposure via clothing is still widespread. Historically metal exposure through clothing played an important step in the overall understanding of ACD; notably, the multitude of cases of suspender and garter dermatitis in the 1950s and blue jean button dermatitis in the 1970s and 1980s brought nickel ACD and contact dermatitis in general closer to the forefront of academic dermatology.

13.5.1 Leather

Perhaps the most common source of metal exposure via clothing is exposure to chromium and cobalt in leather products. Trivalent chromium (Cr[III]) has been used in the leather tanning process since the middle to late 1800s and is favored over vegetable or other mineral-based tanning due to its simplicity, cost-effectiveness, and more consistent performance [96]. It is estimated that 80–90% of worldwide tanned leather is tanned using chromium sulfates [97, 98]. Cr(III) is also used in secondary tanning, dyeing, and processing of leather products. Typically, chromium allergy is tested for using patch tests containing hexavalent chromium (Cr[VI]), and for many decades it was thought that Cr(IV) alone was responsible for clinical chromium allergy; however, new evidence suggests that the less-potent Cr(III) may also play a role [99–101]. While chromium used in the tanning process is universally used in its trivalent form, Cr(VI) is commonly found in finished leathers, likely a result of chromium oxidation secondary to changes in temperature and pH during the tanning process

[102, 103]. Other metal allergens are also occasionally found in finished leather products. Aluminum is infrequently used as a mineral-tanning alternative to Cr(III), but aluminum is a rare allergen and no cases of leather-induced ACD have been reported. Similarly, cadmium, copper, mercury, nickel, and zinc have all been identified in finished leather samples, likely introduced in leather dyes, pigments, pesticides, or as a result of contaminated tanning equipment [98, 104]. Again, there have been no cases of leather ACD to any of these metal allergens; this may be secondary to underreporting, or simply because insufficient levels of these metals are released from the final leather products to elicit ACD.

There have been many exposure studies performed evaluating leather samples and products for chromium content and release. However, given chromium's unambiguous use in the leather process, most of these studies aim to differentiate Cr(III) from the more troublesome Cr(VI) in finished leather and the processes that favor one or another [102, 103, 105–107], or seek to confirm the presence of chromium in leather products suspected to cause ACD [108]. All but a very few have robust selection methods aimed at identifying typical user exposure patterns. A recent study from Bregnbak et al. seeking to validate a new chromium spot test found Cr(VI) in 4/100 leather shoes and 6/11 leather gloves [83]. One study by Rydin et al. in 2002 on behalf of the Danish Environmental Protection Agency found that 15/43 (35%) leather items including watchstraps, baby shoes, gloves, shoes, and other leather clothing contained Cr(VI) above 3 mg/kg [109]. Another identified quantifiable levels of Cr(VI) in 11 out of 11 protective leather gloves [110]. However, when known chromium-sensitive individuals were patch tested with the same leather samples, zero of eight individuals reacted, again emphasizing the important clinical difference between metal content and release. A Swedish study in 2009 found chromium at levels of 42–29,000 mg/kg in 21/21 leather shoes [104]. However, none of the shoes contained detectable levels of Cr(VI). Other exposure studies on leather shoes [111], leather used in car manufacturing [112], and waste products from tanneries have also been performed [98]. The differences in findings between these studies likely reflect both discrepant selection methods, e.g. intentionally only selecting chromium-tanned leathers, and assessment tool used. See Chap. 4 for further information regarding chromium testing.

The most common clinical presentation of non-occupational chromium ACD secondary to leather is foot dermatitis [113]. This clinical presentation was noted in the early 1950s [114–116]. Chromium was also included in one of the first suggested supplementary screening trays, a foot dermatitis tray, proposed in 1959 [101]. Many case reports [117–120] and clinical data have confirmed that chromium is a common culprit for shoe dermatitis [121–124]. Chromium leather ACD has also been reported after contact with leather gloves (most commonly but not exclusively), leather work gloves [108, 115, 125, 126], leather gymnastic wrist supports [127], lederhosen [128] and increasingly, leather furniture [129, 130].

The only other metal allergen that has been shown to cause leather ACD in end-users is cobalt, and this is a relatively new clinical finding. Leather cobalt ACD was first reported in 2013 in a 66-year-old male who developed near-generalized dermatitis secondary to cobalt exposure in his leather sofa [131]. This 2013 study was also the first exposure study seeking to evaluate cobalt release from leather products. They found that 1/14 (7%) leather furniture samples from a single Danish furniture store contained cobalt, and all contained chromium by X-ray fluorescence spectroscopy. Previous exposure studies evaluating leather shoes and other items have identified cobalt content in leather but not specifically with regard to risk of ACD in the end consumer. Namely, a Swedish study that found detectable levels of cobalt in 20/21 (95%) leather shoes [104]. Another recent study found that 20/131 (15%) leather furniture samples contained cobalt by X-ray fluorescence spectroscopy [12]. Unfortunately, there is no reliable cobalt release measurement tool that can be used on leather. It is likely that cobalt is introduced into leather in the form of pigments during the leather dyeing process [132].

ACD to cobalt in leather is likely underreported given its novelty in the medical literature. As such there are currently only two case reports published, the case discussed previously and a

case of a child who developed pretibial dermatitis from a leather chair [133]. However, clinical data on shoe dermatitis [124] and among leather workers [134, 135] has noted increased cobalt sensitization for many years. Additionally, in some of the reported leather chromium ACD cases, authors note a concomitant reaction to cobalt, perhaps representing co-sensitization via leather exposure [118, 119]. Further emphasizing the likely role cobalt has in clinical leather ACD, a recent questionnaire-based case–control study on 183 dermatitis patients with positive patch test reactions to cobalt chloride and negative patch test reactions to potassium dichromate were more likely than controls to report non-occupational dermatitis caused by leather exposure [136].

13.5.2 Textiles

Metals are seldom the culprit in textile dermatitis. However, metal textile dermatitis has been reported. Metals are used in textile manufacturing in the form of complex dyes, oxidizing agents, dye stripping agents, fastness improvers, and finishers [132]. Additionally, some raw textile materials such as cotton, flax, and hemp may naturally contain trace levels of metals accumulated via bio-absorption. However, these levels are typically far below ACD elicitation or sensitization rates at levels typically below 10 mcg/g and often below 1 mcg/g [137, 138]. Allergenic metals that have shown to be contained in some finished textiles include nickel, cobalt, copper, chromium, mercury, and others [139, 140].

The most relevant source of metal exposure via textiles are textile dyes. In particular, chromium, cobalt, copper, and nickel are used in metal complex dyeing, for wool, nylon, cotton, and leather [132, 139, 141]. Chromium-based dyes are used extensively in wool and nylon dyeing; in fact, all mordant wool dyes contain chromium [141]. Despite their known environmental risks and potential, if infrequent, to cause contact allergy, these metals continue to be used in textile manufacturing because they are the most efficient and at times the only method to achieve certain hues in the final product, namely turquoise, brilliant green, and some violet, blue and navy shades [141].

Reports of textile-induced metal dermatitis are rare, and many of the reported cases are decades old. It is not clear if this is because of a reporting bias or a general decrease in dyes that use chromium and cobalt in favor of the more environmentally friendly iron [142]. Chromium ACD from textiles was reported as early as 1948 in a case series of men who developed dermatitis to khaki clothing thought to be secondary to chromium-based dyes [143]. Cr(III) was extracted from textiles that caused chromium ACD in two Swedish military servicemen [144]. Military uniforms were also reported to cause chromium sensitization and dermatitis in Nigeria [145]. In a Korean case report, chromium-based dyes were suspected of causing dermatitis to a dark-colored bra [146]. Another case report highlights a nurse practitioner who developed cobalt ACD to her blue cobalt-dyed scrub pants [147]. Chromium textile ACD has also been reported after contact with men's trousers, women's outerwear, and a woman's dress [128, 148]. Clinical reporting of textile dermatitis often highlights contact allergy to disperse blue dyes and other non-metal allergenic dyes. However, high rates of chromium patch test reactivity are sometimes noted in these clinical reports, possibly representing either misdiagnosis or co-sensitization. For example, in one cohort of 82 patients with clinical textile ACD who reacted to one or more allergens in a textile colors and finish series, 13% also reacted to potassium dichromate [149]. Likewise, in some textile ACD case report/case series thought to be secondary to non-metal dyes, concomitant reactions to cobalt or chloride are noted but rarely commented on [150, 151].

13.5.3 Clothing and Belts

Metals are frequently found in the snaps, rivets, buckles, and clasps used in clothing and have been extensively documented as elicitors of metal ACD. In fact, metal exposure via clothing snaps, buckles, rivets, and clasps has historically played a large role in driving clinical contact allergy. While the bulk of nickel contact allergy in the early 1900s was driven by occupational exposure, in the 1930s through 1950s there was a

proliferation of nickel use in consumer products [152]. Case reports of ACD to clasps on stocking garters were first published in the 1930s [41]. ACD from stocking suspenders or garters was reported through the 1950s [14, 152–154]. For the most part nickel was the offending allergen in these cases; however, chromium garter dermatitis was also reported [155]. Nickel ACD was also reported to corset fasteners, bra clasps, and suspenders [14, 41].

With changing styles and types of clothing commonly worn, stocking garter dermatitis became less and less prevalent, but the use of metals in clothing clasps, snaps, and buttons did not. Beginning in the 1970s, ACD from metal release from pants buttons and rivets began to be reported [156]. Classically this clinical picture was periumbilical dermatitis secondary to nickel release from metallic blue jeans buttons [156]. In 1979 Brandrup and Larsen presented a case series of 79 nickel allergic patients with clinically relevant dermatitis from contact with blue jeans buttons [156]. Ten blue jean buttons brought in by patients were tested by DMG and seven were found to release nickel. This study's novel combination of clinical reporting and exposure evaluation by the relatively new DMG method prompted a series of exposure studies in 1979 and the early 1980s (see Table 13.2; Fig. 13.4) [4, 76, 157].

Table 13.2 Exposure studies evaluating metal clothing items for metal ion release

Sources—selection criteria	Country	Metal	Method of detection—number positive (%)	Citation
Metal buttons from used blue jeans	Denmark	Nickel	AAS[a]-based synthetic sweat method at 2 different temperatures—2/10 (20%)	Menne and Solgaard [4]
Metallic buttons from blue jeans suspected of provoking contact dermatitis	Denmark	Nickel	DMG—7/10 (70%) AAS[a]-based synthetic sweat method—5/10 (50%)	Larsen and Brandrup [157]
Metal clothing items, predominantly blue jeans buttons but also, a zipper, bra hook, garter hook, and shoe buckle, of total 25 items 9 were not and 16 were tolerated by nickel-sensitive subjects	France	Nickel	DMG—9/25 (36%)	Cavelier et al. [76]
Metal components from various items of clothing, as well as buttons, zippers, buckles, clasps, and shoes	Sweden	Nickel	DMG—94/281 (33%)	Lidén and Johnsson [78]
Metal buttons from blue jeans	United States	Nickel	DMG—9/90 (10%)	Byer and Morrell [170]
Metal components from various items of clothing, as well as buttons, zippers, buckles, clasps, and shoes	Sweden	Nickel	DMG—19/276 (6.9%)	Lidén and Norberg [79]
Buttons from new and pre-worn blue jeans	United States	Nickel	DMG—10/62 (23%)	Suneja et al. [169]
Clothing fasteners (2 buttons, 1 hook clasp)	South Korea	Nickel	ICP-AES[b] and synthetic sweat release—3/3 (100%)	Kim et al. [80]
Pediatric clothing fasteners	United States	Nickel	DMG—10/173 (6%)	Heim and McKean [192]
Metal items from a wide range of clothing types including jackets, jeans, sweaters, trousers, sewing materials intended for clothing use including buckles, buttons, and zippers	Sweden	Nickel	DMG—7/139 (5.0%)	Biesterbos et al. [33]

(continued)

Table 13.2 (continued)

Sources—selection criteria	Country	Metal	Method of detection—number positive (%)	Citation
Metal items from a wide range of clothing types including jackets, jeans, sweaters, trousers, sewing materials intended for clothing use including buckles, buttons, and zippers	The Netherlands	Nickel	DMG—12/177 (6.8%)	Biesterbos et al. [32]
Snaps from clothing currently being used by 15-year-old schoolchildren	Poland	Nickel	DMG—25/219 (11%)	Krecisz et al. [82]
Metal clothing items including buttons, hooks, snaps, studs, zippers, and other metal accessories for clothing	Korea	Nickel, cobalt	DMG—58/76 (76%) cobalt spot test—11/76 (15%)	Cheong et al. [16]

[a]AAS—atomic absorption spectroscopy
[b]ICP-AES—inductively coupled plasma optical emission spectrometry

Fig. 13.4 Positive DMG test from a nickel-releasing jeans button

Further exposure studies conducted in the 2000s expanded to also evaluate zippers, buckles, clasps, and other metallic clothing components. Studies that investigated articles of clothing suspected of causing nickel ACD show high rates of nickel release. Studies that investigated convenience samplings of metallic clasps, buttons, rivets, etc. found a wide range of nickel release rates, from ~5 to ~75% of items releasing nickel. This wide range likely represents differences in sampling methods between studies, changes in clothing production through time, and changes in clothing types and styles tested. Only one recent study evaluated cobalt release from clothing snaps, rivets, and other accessories and found that 11/76 (15%) items released cobalt, compared with 58/76 (76%) that released nickel [16]. Exposure studies evaluating clothing snaps, rivets, buttons, and other accessories for other metal allergen content or release have not been performed.

As previously discussed, exposure to nickel-releasing jewelry, and in particular earrings, represents the most important source of nickel exposure and nickel sensitization for both pediatric and adult populations. However, clothing snaps, rivets, and other accessories, in particular, seem to play a large role in pediatric nickel ACD elicitation. The majority of periumbilical dermatitis patients in Brandrup et al.'s original case series were below thirty years of age and many were younger than 20. In 1999 the clinical syndrome of prominent pruritic periumbilical papules was described by Rencic et al. She proposed that this clinical picture could be used as a possible diagnostic criteria for pediatric atopic dermatitis diagnosis [158]. However, after publication, four letters to the editor were published strongly suggesting that prominent pruritic periumbilical papules were characteristic of nickel ACD in their pediatric populations [159–162]. Also in response to Rencic's clinical syndrome, Sharma et al. published a case series in 2002 describing 38 children with "prominent pruritic periumbilical papules," all who were nickel allergic. Other case series have illustrated that periumbilical dermatitis is common in children with nickel allergy

[163]. And other case reports have highlighted periumbilical excoriated papules as a common presentation of pediatric nickel ACD from metal buttons [164–166]. Additionally, clinical studies on general ACD in children often identify nickel as a frequent contact allergen and cite metallic snaps as a possible culprit [167, 168].

Clinically, it is sometimes recommended that patients with nickel ACD from clothing snaps or buttons apply a coat of nail polish to the offending item [168]. This technique seems effective at preventing nickel release, even after up to seven wash-dry cycles in a standard washer/dryer [169]. Interestingly one study showed that buttons and snaps on pre-worn jeans released less nickel compared with new jeans [169]. Another study showed that ten DMG-negative snaps on jeans remained DMG-negative after washing [170]. There is some evidence that smooth metal buttons may release more nickel than ridged buttons [170].

In part stimulated by these studies documenting "prominent pruritic periumbilical papules," the role of metal belt buckles was raised as another contributing element in this clinical picture. In particular, in 2004, Byer and Morrell evaluated both jean snaps and belt buckles for nickel release and found that over 50% of belt buckles released nickel compared with 10% of jean buttons (see Fig. 13.5) [170]. Belts had previously been evaluated for nickel release by Lidén and Johnsson in 2001 as a part of a larger survey of nickel release from various metallic items available for purchase in Sweden [78]. Since then belt buckles have been evaluated in many exposure studies (see Table 13.3). Nickel release was found in between ~40% and ~80% of belt buckles evaluated across eleven studies.

Belts have also been evaluated for possible cobalt release; other than two Asian studies, one in South Korea [16] and one in Thailand [52] that found 40% of 21 and 29% of 28 belt buckles to release cobalt, cobalt was not identified in more than 1% of belts [51, 171]. It is unclear if the large differences between these results reflect differences in belt cobalt release in different international markets or simply variability in selection criteria and testing methodology. Of note, cobalt

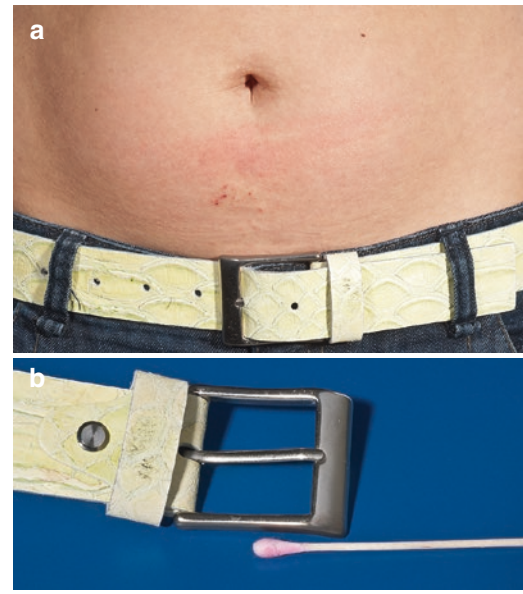

Fig. 13.5 (**a**) An adolescent with pruritic periumbilical papules secondary to nickel exposure via a belt (**b**) Positive DMG test from nickel-releasing belt

allergy is very common in Thailand, with some reports as high as 16%, perhaps reflecting increased sensitization from belt exposure [172].

Despite the relatively high prevalence of nickel release from belts and belt buckles, there are few clinical data published on nickel ACD secondary to belt exposure. This is likely secondary to a perceived lack of novelty, but may reflect an actual dearth of clinical cases. One recent case series described 11 nickel allergic patients with relevant nickel-releasing belt exposure [173]. Another case series published in 2003 documents 20 patients with nickel allergy and relevant exposure to either metallic belts or clothing snaps [174]. Among 204 nickel allergic patients in a large cohort from Singapore, clinically relevant exposure to belts was identified in 36 (18%) [175]. Case reports have also been published illustrating the possibility of nickel ACD-induced periumbilical dermatitis [176–182]. Interestingly, however, most of these case reports are case reports of nickel ACD at other sites, e.g. mobile phone preauricular ACD, in which the authors also note a periumbilical dermatitis and presumed belt-induced ACD. Despite the relatively infrequent clinical reports of belt ACD, avoidance of

Table 13.3 Exposure studies evaluating belts and belt buckles for metal ion release

Sources—selection criteria	Country	Metal	Method of detection—number positive (%)	Citation
Belt buckles	Sweden	Nickel	DMG—18/45 (40%)	Lidén and Johnsson [78]
Belt buckles	USA	Nickel	DMG—25/47 (53%)	Byer and Morrell [170]
Belt buckles	South Korea	Nickel	ICP-AES[a] and synthetic sweat release—2/2 (100%)	Kim et al. [80]
Belts and belt buckles	Sweden	Nickel	DMG—14/57 (25%)	Biesterbos et al. [33]
Belt buckles with possible clinical relevance to nickel-allergic patients	Denmark	Nickel	DMG—2/3 (67%)	Thyssen et al. [81]
Belts and belt buckles	The Netherlands	Nickel	DMG—23/88 (38%)	Biesterbos et al. [32]
Belts and belt buckles	United States and China	Nickel, cobalt	DMG—406/701 (58%), cobalt spot test 5/701 (0.7%)	Hamann et al. [51]
Belt buckles currently being used by 15-year-old schoolchildren	Poland	Nickel	DMG—74/130 (56%)	Krecisz et al. [82]
Belt buckles	South Korea	Nickel, cobalt	DMG—17/21 (81%), cobalt spot test—6/21 (29%)	Cheong et al. [16]
Belt buckles	Thailand	Nickel, cobalt	DMG—12/28 (43%), cobalt emersion test[b]—3/28 (29%)	Boonchai et al. [52]
Belt buckles	South Korea	Nickel, cobalt	DMG—45/91 (50%), cobalt spot test—0/91 (0%)	Kwon et al. [171]

[a]ICP-AES—inductively coupled plasma optical emission spectrometry
[b]Cobalt emersion test—emersion of test items in cobalt spot test solution for 5 min

metallic belt buckles is often highlighted in more general ACD guidelines [168, 183]. While belts may contain cobalt and other allergenic metals, to our knowledge there have been no reported cases of ACD to any other metals from belts.

13.5.4 Other Clothing Exposures

The most common routes of exposure to nickel, chromium, and other allergenic metals in clothing are via leather, textiles, clothing snaps, buttons and belts; however, more esoteric exposure sources have also been reported. ACD from nickel and cobalt secondary to exposure via dyes used in plastic shoes has been reported [184], as has systemic ACD to mercury after contact with mercury containing ply-vinyl boots [185]. Metal charms on bras as well as bra clasps have been reported as sources of nickel ACD [14, 186, 187]. More recently a bra underwire was reported as a cause of nickel ACD elicitation [188]. Metallic threads used in traditional Indian embroidery have also been reported to cause nickel ACD [189, 190]. Other clothing accessories such as handbags, wallets, and umbrellas have been shown to release nickel but no case reports illustrating their clinical significance have been published [191].

13.6 Metals and Technology

Mobile phones, computers, handheld tablets, and other modern technological devices represent a new source of exposure to metals in everyday life. These devices may contain and release metal and can cause ACD. In particular ACD secondary to metal exposure in mobile phones is increasingly common [193].

13.6.1 Mobile Phones

Mobile phone use is exceedingly common. Over 95% of Americans own mobile phones, and over 70% own smartphones [194]. Nickel ACD from a phone was first reported in 1985 in a nickel-allergic patient who reacted to her nickel-releasing phone receiver [76]. Mobile phone ACD was first reported by Pazzaglia in 2000 in a small case series of nickel-allergic patients with relevant nickel-releasing cell phone exposure [195]. Since then there have been over twenty case series or case reports describing ACD from metal release from mobile phones. These are clearly documented in a recent review article (see Fig. 13.6, Table 13.4) [193].

The most commonly clinical presentation of mobile phone dermatitis is, unsurprisingly, facial dermatitis. Both unilateral [195–204] and bilateral [182, 202, 204, 205] facial dermatitis have been reported; more specifically, the distribution is typically preauricular, buccal, or mental, however auricle and tragus involvement has also been reported [197, 205]. More atypical presentations include thigh dermatitis secondary to storage of the offending mobile phone [182] and breast or chest dermatitis in women who secure their phone inside their bra [206, 207]. In general nickel is most often identified as the offending allergen [195, 198–201, 204–207]; however, chromium is also a frequent culprit [196, 197, 203, 204]. Many of these patients presented with other manifestations of nickel allergy, for example concomitant umbilical dermatitis from contact with belt buckles [181, 206], or wrist dermatitis from contact with a nickel-releasing watch band [180]. Bluetooth headsets [202] and metallic phone cases [208] have also been reported to cause nickel ACD. Most mobile phone metal ACD is from normal everyday use; however, occupational cases have been reported [180, 182, 199]. Metal ACD from mobile phones disproportionately affects younger patients. A recent review estimated that ~40% of reported mobile phone dermatitis cases were in patients under 18 [193]. If occupational cases were removed, this estimate would increase greatly.

There are no clear cases of non-nickel, non-chromium mobile phone dermatitis. In one case series a patient with mobile phone ACD tested positive to chromium, the suspected contact allergen, but also to cobalt [197]. In that case the offending phone was not tested for chromium or cobalt release or content. In the same series two patients had doubtful positive reactions to indium; again chromium allergy was the presumptive diagnosis [197]. In another case series a nickel allergic patient with mobile phone ACD also reacted to palladium, a known nickel

Fig. 13.6 Positive DMG test from a nickel-releasing mobile phone

Table 13.4 Exposure studies evaluating mobile phones for metal ion release

Sources—selection criteria	Country	Metal	Method of detection—number positive (%)	Citation
Mobile phone components	South Korea	Nickel	DMG—22/104 (22%)	Kim et al. [204]
Mobile phones and bluetooth handsets	United States	Nickel	DMG—4/22 (18%)	Luo and Bercovitch [179]
Mobile phones	Denmark	Nickel	DMG—8/41 (20%)	Thyssen et al. [199]
Mobile phones	Denmark	Nickel	EN1811[a]—5/20 (25%)	Pors et al. [212]
Mobile phones	Denmark	Nickel	DMG—1/20 (5.0%)	Danish EPA [213]
Mobile phones with possible clinical relevance to nickel allergic patients	Denmark	Nickel	DMG—8/26 (31%)	Thyssen et al. [81]
Randomly selected mobile phones currently for sale in Denmark	Denmark	Nickel	DMG—9/50 (18%)	Jensen et al. [214]
Randomly selected mobile phones	Denmark	Cobalt	Cobalt spot test—0/50 (0%)	Thyssen et al. [210]
Top selling mobile phones	United States	Nickel, cobalt	DMG—24/72 (33%), cobalt spot test—10/72 (14%)	Aquino et al. [211]
Mobile phones and other telecommunication devices	United States	Nickel, cobalt	DMG—21/50 (42%), cobalt spot test—0/5 (0%)	Hamann et al. [215]
Mobile phones	Sweden	Nickel	DMG—5/13 (38%)	Ringborg et al. [191]

[a]EN 1811—an established reference method for establishing nickel release from items intended to come into prolonged contact with the body, based on a 7-day synthetic sweat bath and analysis with atomic absorption spectroscopy, inductively coupled plasma mass spectrometry or other appropriate technique [85]

cross-sensitizer; however, palladium content of the offending phone was not investigated [209]. In a third case series three individuals with mobile phone dermatitis tested positive to both nickel and cobalt; all three were given a diagnosis of nickel ACD but the phones were not tested for nickel or cobalt release or content [181].

Most case reports of nickel mobile phone dermatitis described above used the DMG technique to confirm nickel release. The first systematic evaluation of nickel exposure via mobile phones was performed in South Korea by Kim et al. [204] They found that 22% of 104 metallic mobile phone components released nickel. Other exposure studies in the United States and Europe found between ~5% and ~40% of mobile phones to release nickel. Two exposure studies evaluating mobile phone cobalt release found it in 0% of 50 and 14% of 72 phones in Denmark and the United States, respectively [210, 211].

It is clear that traditional mobile phones, in contrast to so-called "smartphones," release more nickel, and possibly more cobalt. This is evidenced by exposure studies [211], as well as the paucity of clinical cases of smartphone ACD, in contrast to the slew of traditional phone ACD reports [179, 180, 195, 198, 201–203, 205, 209]. There are multiple possible explanations for this phenomenon. The most simple is that changes in phone design and production are resulting in phones that release less allergenic metal. A second possibility is that the European Nickel Directive limiting the amount of nickel that can be released from items in prolonged contact with the skin to 0.5 mcg nickel/cm^2/week was extended to include mobile phones in 2009, thus prompting a change in mobile phone manufacturing practices [216]. It is also possible that the discrepancy in smartphone vs. traditional mobile phone metal ACD reporting is secondary to a publication bias

that reduces continued mobile phone ACD reporting due to perceived un-originality. Interestingly it has been reported that the relatively new iPhone5 does, in fact, release nickel [217].

13.6.2 Laptops

The first case of metal laptop ACD was published in 2012 by Jensen et al. He described a case of a 50-year-old woman who developed a pruritic vesicular dermatitis on the ulnar surfaces of both hands after extensive use of a Macintosh laptop. The laptop released nickel by DMG testing and she was found to be nickel allergic [6]. A second case was reported two years later in a 11-year-old boy with recalcitrant generalized dermatitis most severe on the wrists and antecubital fossae found to be allergic to his nickel-releasing laptop [218].

Prompted by this first case report, an exposure study focusing specifically on Macintosh brand laptops was performed in 2012. It found that 7/20 (35%) MacBook laptops released nickel. Interestingly the 20 different models encompassed only 3 different models [7]. No explanation for these discrepant results was offered in the original study; however, none of the seven nickel-releasing laptops were over one-year-old in contrast to the 9 of 113 (69%) non-nickel-releasing laptops that were 2 years or older—suggesting that Macintosh laptops may release less and less nickel as they are used. A more recent laptop exposure study evaluating laptops from five different brands found that 12/31 (39%) released nickel by DMG testing and 2/31 (6%) released cobalt by the cobalt spot test [219]. Similar to the previous study only 8% (1/12) of the nickel-releasing laptops were 2 years or older, in contrast to the 68% (13/19) of the non-nickel-releasing laptops. Additionally, in this study one nickel-releasing laptop was tested in the same location repeatedly with the DMG test and after ten testing cycles the laptop no longer released nickel at that location, further evidencing that nickel is likely used predominantly in surface layers of these laptops and may wear off after prolonged use. A third laptop exposure study performed in Sweden found that 13/14 (100%) of laptops released nickel by DMG testing [191].

Two studies have evaluated computer mice for nickel release. In one, six Macintosh computer mice were evaluated for nickel release and all were positive [7]. In the second, 1/8 (13%) computer mice from 5 different brands released nickel by DMG. No clinical metal ACD from computer mice has yet been reported; other allergens such as phthalates and acrylates have been reported as causes of computer mice ACD [220].

13.6.3 Other Technological Devices

Like mobile phones and laptop computers, other technological devices such as tablets, fitness trackers, and videogame systems are increasingly ubiquitous. However, given their relative novelty in modern society there is relatively little in the way of clinical or exposure studies published. Generalized dermatitis thought to be secondary to nickel ACD from a nickel-releasing tablet was reported in an 11-year-old boy [221]. In another case report, worsening atopic dermatitis in a 9-year-old boy was attributed to nickel ACD from a nickel-releasing button on an Xbox controller [222]. No systematic exposure studies evaluating tablets or video game systems have yet been performed, nor have any robust case series been published.

Wearable fitness trackers have received much attention in the media due to perceived skin intolerance and possible allergic reactions. The popular fitness tracker Fitbit issued a recall in 2014 at first thought to be secondary to nickel ACD but eventually confirmed by the manufacturer to be primarily an issue with ACD to acrylates used in the band adhesive (http://www.fitbit.com/dk/forcesupport, last accessed January 2017). It seems like none of these cases, however, were ever published in the medical literature. Similarly, no confirmed metal ACD cases to wearable

fitness trackers have been reported. Contact urticaria has been reported after contact with an Apple brand smart watch but neither the watch nor patient was tested for nickel release/sensitivity [223]. One recent exposure study did find that 1/8 (13%) selected wearable fitness trackers did release nickel [191], given that nickel release from watches can elicit ACD in nickel-sensitive individuals, it is not unlikely that nickel-releasing fitness trackers may as well [20, 41, 180].

13.7 Specific Pediatric Concerns

The pediatric population seems to be at particular risk of metal ACD from daily-use objects. Nickel ACD in children is especially common in the United States, with estimates of nickel contact allergy over 25% in some populations [224], compared to ~20% or lower in pooled pediatric and adult populations [225]. This relationship is similar in Europe where estimates of nickel allergy prevalence are ~5% higher in pediatric versus pooled populations [226, 227]. Additionally, pediatric patients seem disproportionately represented in metal ACD case reports from daily-use objects, e.g. the majority of clothing snap ACD cases, laptop ACD and mobile phone ACD cases are reported in children.

Toys are an additional metal exposure source relatively unique to children. Toys were first noted in the literature in 2009 as a potential cause of nickel exposure in children, when a plush toy and toy purse were found to have nickel-releasing components by DMG testing [228]. This prompted a second study that found nickel released from a harmonica and other toy instruments [229]. The first large scale exposure study seeking to assess metal ion release from children's toys was performed in 2014 and found that 73/212 (34%) of toys with metal components purchased from 8 different retail and online stores in the United States and Denmark released nickel by DMG [230]. None released cobalt. This exposure study also described three cases of nickel toy ACD, and is, to the best of our knowledge, the first report of toy metal ACD. Since then another case of metal ACD has been reported: copper ACD in a child who often played with copper-containing die-cast cars [89]. Another exposure study found 11/24 (46%) of metallic toys and toy jewelry available for purchase in the United States contained over 930 mg/kg nickel (the EU limit for scrapped toy material) [231]. Interestingly, this study also found significant chromium content (968 mg/kg) in red paint scrapings from a toy car. An exposure study performed on textile-containing toys in Turkey found that 9/9 (100%) of toys contained nickel at levels of 0.4–21.11 mg/kg by atomic absorption spectrometry, although they did not test for nickel release [232]. Toy make-up has also been assessed for allergenic metal content; an Italian study that analyzed 52 toy make-ups with atomic absorption spectroscopy found more than 5 ppm of nickel in 14/52 (27%), more than 5 ppm of chromium in 28/52 (54%), and over 5 ppm of cobalt in 5/52 (10%) toy make-ups [233]. Other specific pediatric everyday use objects known to cause metal ACD include studs on school chairs [234–236], orthodontic equipment [237], school-issued musical instruments [238], and pediatric sports equipment [150]. More general pediatric metal allergy is discussed further elsewhere (see Chap. 37).

13.8 Conclusion and Clinical Considerations

Items with prolonged skin contact, such as jewelry, are more common sources of relevant metal allergen exposure, compared to items with intermittent or transient contact, such as toys or keys. Exposures also are constantly changing, and a permanent definitive list of metal exposures is impossible. However, common metal allergens may be found in many daily-use objects which the clinician should keep in mind (see Table 13.5). Additionally, occupational and consumer exposures may overlap, so basic understanding of occupational metal allergy may also inform consumer metal allergy. In short, metal allergy is very common and clinicians should investigate any metallic item or dyed item as a potential source of exposure to consumers with positive metal patch tests.

Table 13.5 Confirmed or suspected sources of allergenic metal ion exposure in daily-use objects, in relative order of importance

Nickel	Chromium	Cobalt	Gold
Jewelry, watches, and eye-glasses	Consumer leather products: Leather gloves, steering wheels, couches, cushions, leather clothing, shoes, belts, purses, etc.	Consumer leather products: Leather gloves, couches, cushions, leather clothing, shoes, etc.	Jewelry, watches, and eye-glasses
Belts and other clothing items: Zippers, snaps, buttons, rivets	Dental alloys and other medical devices and implants	Dental alloys and other medical devices and implants	Dental alloys and other medical devices and implants
Toys	Cements and other construction materials	Tools	Luxury food products
Tools, scissors	Treated woods and plywood	Cosmetics	
Electronics: Cellphones, computers, gaming devices, other handheld electronics	Jewelry, watches, and eye-glasses	Paints, dyes, inks, pigments, tattoo ink	
Keys	Cosmetics	Jewelry, watches, and eye-glasses	
Dental alloys and other medical devices and implants	Stainless steel items	Nail lacquer	
Stainless steel items	Paints, dyes, inks, pigments, tattoo ink		
Musical instruments			
Cosmetics			

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Metals in Tools and the Workplace

14

Vera Mahler

14.1 Introduction

The use of work tools and their production has been of central importance to the development of humankind. In the modern manufacture of tools, nickel, chromium and cobalt are often used because of their hardening properties and ability to inhibit corrosion, thereby improving quality [1].

Based on a wide range of studies, a non-sensitizing nickel concentration of 0.5 μg/cm²/week has been suggested for consumer items made of nickel alloys [2]. Elicitation of nickel dermatitis was found to be unlikely for concentrations <0.1–1 μg/cm² during occluded exposure and 15 μg/cm² when nonoccluded [2]. Highly sensitized individuals might react to 0.5 ppm nickel (= 0.00005% = 0.5 μg/g ≙ 0.0075 μg/cm²) when exposed to inflamed skin under occlusion [2].

The European Union (EU) nickel directive (Directive 94/27/EC) [3] and subsequently the REACH Regulation (Commission Regulation (EC) No. 552/2009) [4] item 27 of Annex XVII, in force since 1 June 2009, regulates the maximum allowable amount of nickel release from metallic objects intended to come into direct and prolonged contact with the skin: they should not release >0.5 μg nickel/cm²/week [3, 5–7]. "Prolonged skin contact" has been defined, according to the European Chemicals Agency, as 3 exposures of 10 min or 1 exposure of 30 min of skin contact within 2 weeks [8].

Handheld tools—despite being regularly in prolonged skin contact according to this definition—are not listed in the list of regulated items (which includes earrings, necklaces, bracelets and chains, anklets, finger rings, wristwatches, cases, watch straps and tighteners, rivet buttons, rivets, zips and metal marks, when these are used in garments) given in the former directive and the current REACH Regulation. This leads to room for interpretation and is interpreted differently in different countries: e.g., in Denmark, there is the official understanding that tools are included in REACH due to the duration of skin contact with tools (personal communication, Jeanne D. Johansen). In contrast, in Germany and most other European countries, there is the understanding that tools are not included in the scope of this directive, since tools are not explicitly listed among the examples.

The greatest and most specific metal exposures still occur in certain occupational settings. This chapter provides an overview of the current knowledge on metals in tools and the workplace, with regard to metal allergy. Work-related airborne exposure to metals and epidemiological evidence for lung cancer are not within the scope of this chapter (recommended reading: [9–11]).

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14.2 Metals in Tools

Nickel is ubiquitously present in the earth, water and air. In a recent questionnaire-based survey in nickel-allergic patients, tools were reported to be involved in the initial presentation of nickel dermatitis in 1.4% of women and 5.6% of men, whereas earrings, followed by other jewelry, are still the foremost cause of nickel dermatitis [12].

Only a few studies on metal ion release (nickel, cobalt, chromium(VI)) from tools have been published. The first study, published in 1998, was performed in Sweden. It revealed that 27% of 565 handheld tools with metal parts that came into contact with the skin were found to be dimethylglyoxime (DMG) test (see below) positive, indicating sufficient nickel release to elicit dermatitis [13]. In the same study, the release of other metals (cobalt, chromium, and vanadium) was examined in a subgroup of 30 tools. Analysis of these 30 samples did not detect cobalt release in any of the samples, whereas chromium was detected in 8 samples (27%) and vanadium in 3 samples (10%) [13].

In the second study published in 2011, nickel release was identified from 5% of 200 work tools using the DMG test in Denmark. In eight of ten, positive results were localized to the metal ring located at the end of the grip that acts as a cuff. The positive DMG test results were not related to specific categories of work tools. The cobalt spot test gave no positive test reactions [14].

In a recent study published in 2015, using the DMG test, nickel release was detected in 195 of 600 (32.5%) new handheld tools or small hardware items (nails, screws, screw nuts) purchased in 2013 in Germany [1] (Table 14.1). Nickel release from all parts (grip and functional part of the tool) was found in 10.8% of examined objects, nickel release exclusively from the grip part was found in 12%, and nickel release exclusively from the functional part was found in 9.7% [1]. Nickel release from small hardware items was found in 8.3% (n = 7/84 DMG positive).

Positive nickel test results were nearly twice as frequent from tools "made in Germany" than from tools without a mark of origin. Tools made in other European countries did not release nickel. A correlation was found between price level and nickel release: handheld tools from the low price tercile released nickel significantly more frequently compared to intermediately or highly priced tools [1]. Among tool kits, 34.2% were inhomogeneous concerning nickel release [1].

Cobalt release, assessed using the disodium-1-nitroso-2-naphthol-3,6-disulfonatein-based cobalt spot test, was only detected in six tools (1%): five pliers and one saw [1] (Fig. 14.1).

One study published in 2014 investigated skin exposure and metal release from dental tools and alloys [15]. Cobalt-chromium alloys are used as

Table 14.1 Nickel release from handheld tools and small hardware items in a recent limited market survey from Germany [1]. "Other" tools include cranks, clamps, grips, brackets, scissors and screwdriver electricity testers

Tools	Number tested	Number of DMG test pos.	%
Chisels	n = 41	n = 13	31.7
Files	n = 32	n = 17	53.1
Hammers	n = 30	n = 6	20.0
Lathe tools	n = 121	n = 33	27.3
Nails	n = 26	n = 2	7.7
Nuts	n = 36	n = 3	8.3
Pliers	n = 64	n = 34	53.1
Saws	n = 20	n = 8	40.0
Screws	n = 22	n = 2	9.0
Spatulas	n = 21	n = 6	28.6
Wrenches	n = 156	n = 50	32.0
Other	n = 31	n = 21	67.7
Total	n = 600	n = 195	32.5

Fig. 14.1 Cobalt release from tools is rare: a positive spot test from the functional part of a pair of pliers

casting alloys by dental technicians when producing dental prostheses and implants. Cobalt and nickel release from tools and alloys was tested in this study with the cobalt spot test and the DMG test for nickel. Also, the release of cobalt, nickel and chromium in artificial sweat (EN1811) [16] at different time points was assessed. Analysis was performed with inductively coupled plasma mass spectrometry. Sixty-one tools were spot tested: 20% released nickel and 23% released cobalt. Twenty-one tools and five dental alloys were immersed in artificial sweat. All tools released cobalt, nickel and chromium. The ranges were 0.0047–820, 0.0051–10, and 0.010–160 μg/cm^2/week for cobalt, nickel and chromium, respectively. All dental alloys released cobalt in artificial sweat, with a range of 0.0010–17 μg/cm^2/week, and they also released nickel and chromium at low concentrations. The study demonstrated that sensitizing metals are released from tools and alloys used by dental technicians in amounts that may cause contact allergy and hand eczema [15].

In a follow-up study, the same authors quantified cobalt, chromium, and nickel exposure on the skin and in the air, as well as urine levels, in 13 dental technicians working with tools and alloys that could result in skin and respiratory exposure [17]. The metal skin dose was quantified with acid wipe sampling, and air exposure was monitored by personal air sampling (see below). Spot urine samples were collected for 24 h. Metals were analyzed with inductively coupled plasma mass spectrometry. Before work, cobalt was detected on the skin of ten participants (0.00025–0.0039 μg/cm^2) and chromium (0.00051–0.011 μg/cm^2) and nickel (0.0062–0.15 μg/cm^2) on the skin of all participants. After a 2 h period without handwashing, cobalt- and chromium-exposed participants had significantly higher doses of cobalt (median, 0.15 (0.032–1.6) μg/cm^2) and chromium (median, 0.022 (0.012–0.19) μg/cm^2) on their skin (p = 0.004 and p = 0.003, respectively) than participants who had not been exposed to cobalt or chromium. Cobalt was found in ten air samples (0.22–155 μg/m^3), chromium in nine (0.43–71 μg/m^3) and nickel in four (0.48–3.7 μg/m^3). Metal urine concentrations were considered to be normal. The authors concluded that the cobalt skin doses acquired within a 2 h working interval might potentially elicit allergic contact dermatitis and cause sensitization [17].

A recent market survey using the diphenylcarbazide (DPC) spot test showed no chromium(VI) release from work tools (0/100). However, chromium(VI) release from metal screws (7/60), leather shoes (4/100) and leather gloves (6/11) was observed [18].

From these studies, it can be concluded that the low frequency of nickel release from handheld tools identified in Denmark cannot be taken for granted for the tools of all (European) countries, since in the most recent investigation, an unexpectedly high proportion (23%) of handheld tools currently available in Germany released nickel from the grip. Work tools may therefore still be sources of occupational sensitization and may contribute to the elicitation and maintenance of hand eczema [1]. Cobalt and chromium release from work tools was very rare or absent but was identified to be regularly present from dental tools, in addition to nickel [17].

Occupational metal exposure should be individually assessed in metal sensitized workers and needs to be taken into account for the management of chronic hand eczema [see Chap. 36], as well as for expert medical assessments of work-related hand eczema [1].

14.3 Other Metal Sources in the Workplace

14.3.1 Nickel

Industrially, nickel is frequently used as an alloy constituent, along with other metals and noble metals [19]. Nickel is found in products for both occupational and private use, many of which come into contact with the skin [20]. Depending on their composition (pure nickel metal, nickel-containing alloys, coatings), silvery-appearing tools and other objects from the workplace have a varying ability to release nickel ions upon skin contact and to cause sensitization and dermatitis

[21]. Neither the exact metal/alloy composition of silvery-appearing objects from the workplace or their nickel ion release upon contact with sweat are usually known or provided on material safety data sheets. There is no relationship between the content of nickel in an alloy and its ability to cause an allergic reaction, while there is a close relationship between the rate of ion formation from nickel in the presence of sweat and the potential to cause a skin reaction [20]. The predicted dose required to elicit an allergic skin reaction in 10% of nickel-allergic individuals was calculated to be 0.78 μg nickel/cm^2 in the patch test, whereas the threshold for the repeated open application test (ROAT) in μg nickel/cm^2 per application (which better represents repeated workplace exposures) was significantly lower [22]. Notably, the dose-response for the accumulated ROAT dose at 1 week, 2 weeks, and 3 weeks was very similar to the patch test dose-response curve [23].

Work-related nickel exposure (detected by acid wipe sampling after 1–2 h of regular work) exceeding identified elicitation doses [22, 23] has been found among locksmiths [20, 24], metalworkers [25], cashiers [20, 24, 26], sales assistants [26], carpenters [20, 24], electroplaters [26], and, to a much lower degree, secretaries [20, 24]; furthermore, occupational exposure has been shown in nickel-allergic patients with work-related hand eczema [27]. Out of the many occupations that have the potential for nickel exposure [10, 20], the following nickel exposures have been emphasized [19]:

- Galvanization industry.
- Assembly of nickel-plated parts.
- Work-related, nickel-releasing surfaces in contact with the skin, which have to be determined individually.
- Currently, hairdressers' scissors do not normally release nickel any longer. However, crochet hooks used by hairdressers have been found to still be a frequent source of excessive nickel release [28].

Occupational nickel dermatitis usually presents as hand dermatitis [20]. A vast number of occupational exposures and work-related cohorts at risk of occupational contact dermatitis due to nickel have been published [10, 11, 20, 29, 30] (Table 14.2); however, due to improved industrial hygiene and technical developments, these cannot be extrapolated without restriction to current work-related exposures.

The nickel concentration has been described to be low in unused (<0.1 μg/g) and used (0.1–0.15 μg/g) metalworking fluids [29] including in a recent investigation performed in a socket manufacturing plant on six metals (Cr, Cu, Fe, Mn, Ni and Zn) in unused and used sump metalworking fluid (MWF). In Taiwan, samples of used versus unused MWF did not display significant differences in nickel concentration, whereas samples from thread-cutting machines displayed higher concentrations of chromium, copper, iron, and manganese in sump MWF, and samples from punch press machines displayed higher concentrations of copper, iron, manganese, and zinc in sump MWFs when compared to unused MWFs [31].

In nickel-allergic individuals with a work-related history of hand dermatitis (especially if working in one of the occupations summarized in Table 14.2), a robust individual work exposure assessment is recommended. Exposure reduction is essential [20]. For the diagnosis of occupational nickel sensitization and allergic contact dermatitis, besides contact to a nickel-releasing product, the duration and frequency of exposure, specific circumstances of exposure (e.g., occlusion, pressure), coexisting exposures (irritants, other contact allergens), area of exposure, the degree of individual sensitization and skin barrier integrity at the location of exposure are relevant factors which need to be assessed individually [19–21, 23, 26]. Nickel-releasing (DMG positive) surfaces that have been identified to cause work-related hand eczema have included keys (in psychiatric nurses), electrical components (in an industrial worker), sewing needles (in a dressmaker), bread pans and baking trays (in a sandwich maker) and tools (in a carpenter) [27].

A recent limited market survey in Stockholm identified nickel release from 48% of examined

Table 14.2 Occupational contact dermatitis due to work-related nickel exposure has been reported [20, 29, 30]. Note that, due to improved industrial hygiene and technical developments, this may not be applicable to current workplace exposures, and an individualized assessment is recommended

Occupation	Reported work-related nickel exposures
Automechanic	Tools
Battery production	Anodic electrochromic material
Butcher	Clasps and buttons of protective gloves
Carpenter	Tools, pipes, locks, architectural (anodized) aluminum (e.g., in doors and window frames), other metal items
Cashier	Handling of coins and contaminated bills (the extent of handling coins relevant for elicitation of nickel allergy is not clear, as performed provocation studies resulted in different outcomes)
Ceramic and glassworker	Colorant and catalyst
Chemical industry personnel	Catalyst
Cleaner	Equipment, tools, handles, keys, (detergents: in normal use concentration of 0.1–1% only rarely exceeds 0.1 μg/g)
Dentist	Dental tools and alloys
Dyers	Dye fixative
Electrician	Tools, other metal items
Electronic industry personnel and repairmen	Nickel-plated earthing straps, nickel-plated tools, coolants
Electroplater	Handling of hot nickel salt solutions, contamination of the work environment, working clothes and protective gear
Enamel worker	Nickel components as adherent
Food manufacturer and restaurant personnel	Equipment, vegetables
Hairdresser and barber	In previous times: scissors; current possible nickel sources include crochet hooks, clips
Hospital worker	Equipment, tools, handles, keys
Household worker	Equipment, tools, handles, keys
Jeweler	Nickel-containing alloys, white gold
Locksmith	Tools, pipes, locks, architectural (anodized) aluminum (e.g., in doors and window frames), other metal items
Mechanic and mechanical engineering	Handling of nickel-alloyed or nickel-plated metals (including tools and handles of machines)
Metalworker and welder	Varying nickel exposure depending on department/task (e.g., high nickel exposure in the production of space propulsion structures and thermal application of different metal-containing powders); welding fumes, skin contact with nickel-alloyed electrodes
Musicians	Nickel-releasing metal parts of the instrument
Office worker	Keys
Painter	Pigment and contaminant of paint, tools
Plumber	Tools, pipes, other metal items
Printer	Electroplating solution (printing plates), tools, contaminant of ink/toner
Shop assistant	Handling of coins and contaminated bills (the extent of handling coins relevant for elicitation of nickel allergy is not clear, as performed provocation studies resulted in different outcomes)
Spark plug maker	Spark plug center electrodes feature a copper core, covered in a nickel alloy
Teacher	Nickel-containing chalk
Textile worker	Dye fixative, needles, scissors
Veterinarian	Equipment, e.g., stethoscope

electronic devices (e.g., laptop PCs, 13/13 DMG positive; PC mice, 1/5 DMG positive, 4 doubtful) and 54% of examined utensils (e.g., paintbrushes, 17/28 DMG positive; pens, 5/12 positive, 1 doubtful), all of which may be occupationally relevant [32]. Keys from the workplace or home are a frequent source of nickel release: 80% of recently investigated door keys displayed a positive DMG spot test [33].

To gain information on an individual workplace exposure, a DMG test may be indicative and will enable the introduction of exposure-reducing alternatives [27, 28, 34].

14.3.2 Cobalt

An isolated occupational cobalt allergy is rather rare [35]. Frequently a coexisting contact sensitization to other metals (nickel or chromium) is present [19, 36].

Cobalt is often used in different alloys and hard metals; in orthopedic and dental prosthetics; as a pigment in pottery, glass, and paints; in detergents; in magnets; in cosmetic products; and in many other applications [37, 38]. Occupational contact dermatitis caused by cobalt exposure in hard metalworkers, metalworkers and pottery workers is well known among dermatologists, but cobalt allergy often remains unexplained [39–42]. A recent multifactorial analysis of risk factors for contact sensitization to cobalt based on long-term data from the Information Network of Departments of Dermatology identified construction workers, metal surface treaters, cashiers and printers as high-risk occupations [36].

In a review on current occupational exposures, the following relevant cobalt exposures were identified [19]:

- Direct contact with cobalt-containing metals, metal dusts and used cutting fluids occurs in the metal industries when working with steel or hard metals.
- Cobalt salts (e.g., cobalt chloride, cobalt phosphate, cobalt sulfate or cobalt oxide) are used as blue or green color ingredients in the glass, porcelain, enamel and ceramic industries.
- Cobalt naphthenate or other cobalt salts of organic acids are used as siccatives in paints or drying accelerators in the hardening of synthetic resins.
- Cement containing traces of cobalt may lead to cobalt allergy in masons with preexisting chromium allergy.
- Cases of cobalt sensitization due to exposure to coins [see Chap. 16], cobalt-containing cattle feed, iontophoresis gels and airborne contact dermatitis in diamond grinders due to cobalt-containing grinding discs have been reported.

To prevent sensitization and dermatitis in workers and consumers, legislation limiting the amount of hexavalent chromium in cement and nickel in items intended for prolonged contact with the skin has been enforced and now forms part of REACH [4]. However, no such legislation exists for cobalt [15].

14.3.3 Chromium

The actual hapten is trivalent chromium (Cr(III)), which penetrates the epidermis poorly and binds to proteins of the stratum corneum [see Chap. 7]. Cr(III)-penetration into the deeper epidermal layers and contact with antigen presenting cells is rare [43, 44]. Consequently, occupational exposure to Cr(III) represents a much lower hazard for sensitization and chromium allergy as compared to hexavalent chromium (Cr(VI)), which is water-soluble and easily penetrates the skin, where it is reduced within the epidermis to the actual hapten Cr(III) [43–45].

Chromium-plated surfaces (which have a shiny silver appearance), due to a thin surface layer of insoluble chromium oxide, generally do not release water-soluble Cr(VI) and are thus not regarded as an occupational hazard [46]. Corrosion of chromium-plated items and stainless steel, however, can cause the release of chromium in different oxidation states (mostly chromium(II), Cr(III), and Cr(VI)) [45].

In contrast, handling chromated metal products made from iron or zinc, such as screws, fit-

tings, and other material used in construction and do-it-yourself procedures, must be regarded a hazard to chromium-sensitive individuals, in particular those who are strongly sensitized [46]. The chromating treatment results in a thin surface layer consisting of chromates and hydroxides, providing enhanced corrosion resistance. These chromate layers can appear in various colors, such as yellow, olive, or black [45, 46], and the Cr(VI) released from such chromated products has been shown to vary widely under in vivo and in vitro test conditions: while the Cr(VI) concentration of the supernatant of the yellow and olive items was close to the detection limit, the concentration was about 55 times higher in the supernatant of the black items, which were also capable of eliciting a positive patch test in chromium-sensitive individuals [46].

Elicitation concentrations varied in sensitized individuals: in patch testing, most reacted at 1000 ppm (0.1%) Cr(VI), and a few at concentrations of 5 ppm or less [44, 45].

Allergologically relevant occupational exposure to chromium may mainly occur with [45, 47]:

- Cement
- Electroplating
- Chromium plating
- Chromate conversion coating
- Welding
- Chromated metal parts
- Leather production and processing
- Safety gloves or shoes made from chromium-tanned leather
- Wood impregnation
- Laboratory work (e.g., chemical analytics)
- Less frequently, other occupational environments (see below)

In chromium-sensitized patients, the hands and feet are most prone to be involved both in acute and chronic allergic contact dermatitis caused by chromium [48]. Work-related chromium allergy has been frequently reported to be severe, recalcitrant, sometimes widespread, and of relatively poor prognosis [45]. Chromium exposure and allergy have primarily been associated with construction workers, owing to the presence of Cr(VI) in cement (see below) [49, 50]. As a consequence of regulatory interventions concerning the Cr(VI) content in cement, there has been a shift in many European countries in etiology and epidemiology from an occupational contact sensitization of male preponderance toward a sensitization found predominantly in women in the setting of consumer exposure to non-lined leather garments [45, 51]. Despite this shift in primary chromium exposure to leather articles, in a recent survey, chromium-allergic patients still had more severe and more chronic contact dermatitis than control patients with dermatitis but without chromium allergy [48].

14.3.3.1 Cement

For a long time, contact to cement used to be the most frequent cause of chromium allergy. The addition of iron(II) sulfate during the production of cement reduces Cr(VI) to Cr(III); thus, low-chromate cement produced in this way contains less than 2 ppm Cr(VI) and results in hardly any induction of sensitization and generally no elicitation of contact dermatitis in most sensitized individuals [47]. However, the effect of iron(II) sulfate is limited in time, and therefore low-chromate cement requires an expiration date.

EU directive 2003/53/EC [52] came fully into force in 2005 and regulates the use of cement or cement preparations on the market: cement must contain less than 2 ppm Cr(VI) where there is a possibility of contact with the skin. In controlled, closed, and totally automated processes, skin contact does not occur, and they are exempted. Reducing agents should be used at the earliest possible stage, i.e., at the time of cement production. As a consequence of this directive, a decrease in work-related contact sensitization to chromium in men working in the German building trade (bricklayers, tile setters, etc.) from 43.1 to 29.0% was observed [53]. Logistic regression analysis revealed that patients who had started to work in the building trade after the introduction of low-chromate cement had a significantly decreased risk of chromate sensitization (odds ratio 0.42). In Scandinavia, low-chromate cement had been introduced 20 years earlier, and

similar effects were observed [54]. Besides this legislative hapten reduction, increasing mechanization (e.g., the use of rotary machinery for large-scale mixing of cement), education, and implementation of workplace hygiene policies likely contributed to decreased skin contact to chromium. Other occupational groups, such as leatherworkers, metalworkers and cleaners, are also highly exposed to chromium and at risk for contact sensitization (see below) [47, 55]. In contrast to wet cement, during the demolition and handling of aged cement or concrete, no allergologically relevant chromium exposure occurs since the Cr(VI) is bound and water-insoluble.

Aside from the risk for sensitization, chromates have an irritant quality. If in prolonged skin contact, chromates (mostly in wet cement) may induce toxic reactions leading to necrosis (chrome ulcers, cement burns). The majority of cement burns affect the lower limbs (Fig. 14.2). Apart from the alkalinity of cement (pH 12), relevant factors for developing cement burns are abrasion and occlusion: the skin surface is damaged by the abrasive properties of added particulates (e.g., sand), facilitating penetration of the alkaline mostly ready-mixed cement [56]. Exposure is augmented by occlusion due to wet clothes [56]. A few hours after exposure, burning sensations, pain, erythema and vesicles occur as the initial symptoms, and 12–48 h later, partial- to full-thickness burns characterize the clinical picture [56]. Work accidents and do-it-yourself work without adequate protection are the two major risk factors for cement burns [56, 57].

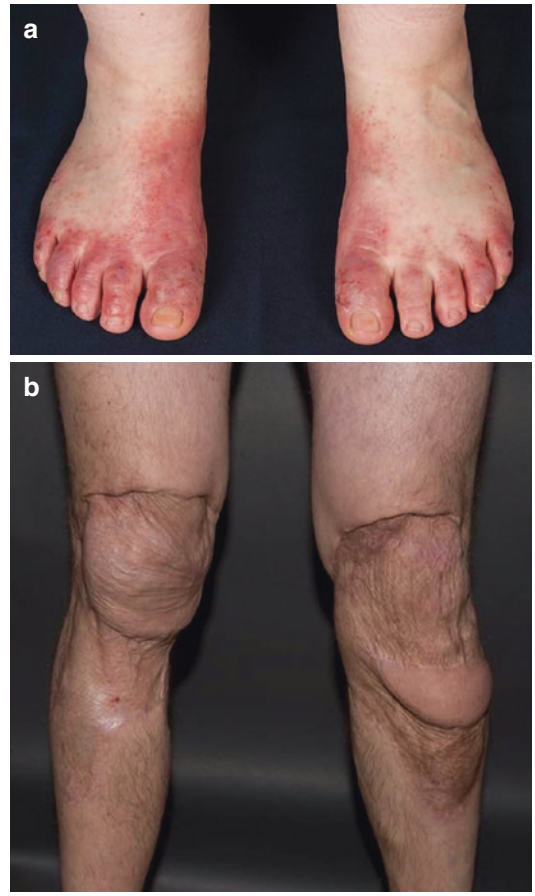

Fig. 14.2 Hazards due to hexavalent chromium: (**a**) Allergic contact dermatitis of the feet due to hexavalent chromium-releasing safety shoes of a kitchen staff member. (**b**) Full-thickness chemical burns in a do-it-yourself constuction worker due to kneeling in wet cement

14.3.3.2 Leather

Leather tanning is performed in most cases with chromium(III) sulfate. A relevant release of Cr(VI) depends on environmental factors such as moisture and pH: with increasing atmospheric humidity, the Cr(VI) release from leather decreases, whereas the Cr(VI) release increases in an alkaline environment (pH 12), e.g., when handling cement [18, 58, 59]. According to the EU Commission Regulation No. 301/2014 [60], in force since 2015, leather articles or leather parts of articles coming into contact with the skin shall not be placed on the market when any of those leather parts contain Cr(VI) in concentrations equal to or greater than 3 mg/kg (3 ppm, 0.0003% by weight) of the total dry weight of that leather part. [For chromate testing in leather, see Chap. 4.] As a consequence of this regulation, a decline in relevance of leather as a source of Cr(VI) sensitization is anticipated. At this point, leather safety gloves exceeding this threshold are still found on the market (author's own investigations).

14.3.3.3 Metal Processing and Handling

Plating and Chromate Conversion Coating

In electroplating, chromium plating, chromate conversion coating, and electrolytic plating, various chromium compounds/chromium salts are in use [47]. In these occupational fields, allergologically relevant exposure to Cr(VI) exists, easily passing through the skin [18, 44, 61].

Metalworking

In contrast to handling chromium-plated surfaces, which do not constitute an allergologically relevant chromium exposure, during welding of chromium-steel alloys, due to oxidizing conditions, an allergologically relevant exposure in welding fumes may occur, leading to reports of airborne allergic contact dermatitis in the older literature [reviewed in 47]. Stainless steel welding process profiling has revealed ways to reduce fume emissions, Cr(VI) emissions, and operating costs in the workplace [62]. Analyses of cutting oils being used during processing of chromium-steel alloys generally demonstrated Cr(VI) concentrations below 1 ppm, with very few exceptions [44, 63].

Chromated Metal Products

Many metal products made from iron or zinc, such as screws, fittings, and other material used in construction and do-it-yourself procedures, are chromated in order to prevent rust or surface oxidation [46]. Their surface is not a shiny silver like that of chrome-plated surfaces, but matte black, yellow, or green. Cr(VI) release in allergologically relevant amounts has been found from their surface [18, 45, 46].

14.3.3.4 Further Occupational Exposures

Currently, chromium exposure is possible by contact to ashes, industrial impregnation of wood, and chrome compounds in laboratory analytics [44, 45, 61, 64]. Chromium exposure due to contact to bleach and cleaning agents, printing, glass polish, wood protection (for topical application), anticorrosion coatings, magnetic tapes, and matches is mostly of historic interest [44, 45, 61, 64]. However, the anticorrosion coatings of metal airplanes nowadays still consist of a chromate-containing paint and primer [47]. Exposure occurs during spray painting and surface grinding. Trivalent chromium salts are used as pigment (e.g., chromium oxide as green pigment) in artist's paints, ceramics, and tattoo colors; a relevant Cr(VI) exposure is probably not present when in contact with these pigments [47].

14.4 Practical Approach to Assess Metal Release from Tools and Other Metal Sources in the Workplace

14.4.1 Nickel Spot Test (Dimethylglyoxime (DMG) Test)

The dimethylglyoxime (DMG) test has been established as a clinically relevant and useful screening method for nickel release and can be used for workplace assessment of nickel release from tools. DMG reacts with nickel salts in the presence of ammonia solution [see Chap. 6]. The detection limit of the DMG test has been estimated to be close to 0.5 μg/cm^2/week [34]. This limit indicates the presence of nickel in sufficient concentrations to elicit nickel dermatitis [34]. However, the moderate sensitivity of the DMG test (determined to be 59.3% (CI 95% = 13.1–46.2%)) needs to be kept in mind, whereas its specificity of 97.5% (CI 95% = 92.7–100%) is very good. For calculation of sensitivity and specificity, true-positive reactions were defined as "positive DMG test reactions that were confirmed by nickel release >0.5 μg/cm^2/week." False-positive reactions were defined as "positive DMG test reactions but with a nickel release concentration below 0.5 μg/cm^2/week." True-negative reactions were defined as "negative DMG test confirmed by a nickel release below

0.5 μg/cm²/week." Finally, false-negative reactions were defined as "negative DMG test reactions but where nickel release was >0.5 μg/cm²/week" [34].

The DMG test has also been shown to be able to detect released nickel on the skin after exposure: positive DMG test reactions occurred in all subjects at the nickel concentrations of 0.50, 0.25, and 0.13 μg/cm² [65].

14.4.2 Cobalt Spot Test (Disodium-1-nitroso-2-naphthol-3,6-disulfonate Test)

A color change of disodium-1-nitroso-2-naphthol-3,6-disulfonate from yellow to red–orange indicates a positive test reaction [see Chap. 6]. The spot test detects approximately 8 ppm cobalt in a solution, a limit close to the lowest elicitation threshold concentration in cobalt-allergic patients [66]. The cobalt spot test has proven to be useful for screening purposes, including cobalt release from cobalt-containing powder in the occupational setting [67].

14.4.3 Chromium (VI) Spot Test (Diphenylcarbazide (DPC) Test)

For the detection of an occupational exposure to Cr(VI), recently a spot test has been established: the diphenylcarbazide (DPC) (1% wt/vol in ethanol)-containing reagent represents a spot test for the identification of Cr(VI) release. It can be used for the detection of chromium on the surface of a solid object, as well as in solutions and powders [see Chap. 6]. It was able to identify Cr(VI) release at 0.5 ppm without interference from other pure metals, alloys, or leather. False-positive test reactions were not found. Confirmatory testing was performed with X-ray fluorescence (XRF) and spectrophotometrically on extraction fluids. The use of DPC as a colorimetric spot test reagent appears to be a valid screening test method for detecting the release of Cr(VI) ions from leather and metal articles [18].

14.4.4 Acid Wipe Sampling and Chemical Analysis

For the assessment of occupational skin exposure to nickel, chromium, and cobalt, acid wipe sampling, performed via cellulose wipes with 1% nitric acid followed by chemical analysis with plasma mass spectrometry, is a very reliable method that has been shown to recover 93% of nickel, chromium and cobalt deposited on the arms and palms [68]. The technique may be used in studies, in dermatitis patients, in the identification of at risk groups, as well as in developing preventive strategies and following up the results of an intervention [68].

14.4.5 Immersion in Artificial Sweat and Chemical Analysis

The release of nickel, cobalt and chromium from tools and other workplace contactants can be studied quantitatively by immersing items in artificial sweat (at 30 °C for 1 week) according to the reference test method for the EU nickel regulation (EN 1811: 2011) [16] and performing chemical analysis of the samples for their metal concentration with mass spectrometry. This method is usually limited to academic research and is not routinely available for occupational exposure assessment on a day-to-day basis.

14.5 Conclusion

Metal release from tools and other workplace materials may pose a risk for occupational contact allergy, especially when surface alteration (cracks due to mechanical use, corrosion, or contact to sweat) occurs. An individualized and timely assessment is required, as identification of the culprit exposure will allow for an appropriate intervention, with a focus on primary and secondary prevention of contact allergy. Spot tests for nickel, cobalt, and chromium may contribute to a simple and feasible occupational exposure assessment.

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Metals in Cosmetics

15

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Abbreviations

Ag Silver
Al Aluminum
As Arsenic
Au Gold
Be Beryllium
Cd Cadmium
Co Cobalt
Cr Chromium
Cu Copper
EU European Union
FDA Food and Drug Administration
Fe Iron
Hg Mercury
Ni Nickel
Pb Lead
Pd Palladium
Pt Platinum
Sb Antimony
Sn Tin
Sr Strontium
Ti Titanium
Tl Thallium
Zn Zinc
Zr Zirconium

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15.1 Introduction

Nowadays, the use of cosmetics constitutes a part of routine body care all over the world. These products are commonly used in order to clean, improve, or alter the skin, lips, hair, nails, and teeth. According to the regulations of the European Union (EU) and some other authorities, cosmetics have to be safe for human health under normal or reasonably foreseeable use, and for each finished product, a safety assessment, including consideration of the toxicological profile of all ingredients, should be performed before its placement on the market [1–4]. In spite of this, some cases of unfavorable health effects have been reported, including most often allergic reactions, resulting from the presence of various chemical compounds in cosmetics [5, 6]. As many as 10,000 chemical substances may be detected in cosmetic products, and there are more than 1000 substances which, due to their toxicological profile, cannot be used in cosmetic products [4, 7]. Among these are several metals.

Due to the presence of metals and their compounds in cosmetics, these products are one of the sources of exposure to various elements. The traditional allergens, such as nickel (Ni), chromium (Cr), and cobalt (Co), as well as other metals which may occasionally or rarely be a cause of allergy, such as aluminum (Al), beryllium (Be), copper (Cu), gold (Au), palladium (Pd), titanium (Ti), iron (Fe), platinum (Pt), tin (Sn), and zinc (Zn), are detected in cosmetics at

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concentrations varying widely from undetectable to as high as several hundred micrograms per gram (~parts per million (ppm)) and sometimes even several milligrams per gram or more (detailed data are presented later in this chapter). Moreover, other nonallergenic metals, including the most toxic heavy metals like cadmium (Cd), lead (Pb), mercury (Hg), and arsenic (As), may be present in these products [5, 6].

Cosmetic preparations are repeatedly applied directly to the skin, mucous membranes, hair, and nails. Thus, metals in cosmetics constitute a source of chronic exposure and may cause unfavorable health effects [5, 6, 8–12]. Moreover, in the case of metal allergens, allergy may occur even after short cosmetic usage and even after the first use in the case of sensitized individuals [8]. For these reasons, in recent years, a growing interest in cosmetics as a source of exposure to toxic metals and secondary unfavorable reactions has been observed [5, 6, 9, 12–20]. It is well known that cosmetics belong to the group of household products most often causative of allergic reactions [9, 11, 21, 22], but until now insufficient attention has been paid to metals in these preparations as a cause of allergy. Thus, this chapter provides an overview of cosmetics as a source of exposure to metals, with particular emphasis on metal allergens whose presence in cosmetics may be a cause of sensitization.

15.2 Overview: Sources of Metals in Cosmetics

Sources of metal exposure in cosmetic products can be broadly divided into two main categories (Fig. 15.1). First, those meant for intentional use in cosmetics production include pigments, UV filters, and preservatives, as well as antiperspirant, antibacterial, and antifungal agents. These include mainly chromium, iron, aluminum, zinc, titanium, strontium (Sr), copper, silver (Ag), and gold, and their use is dependent on

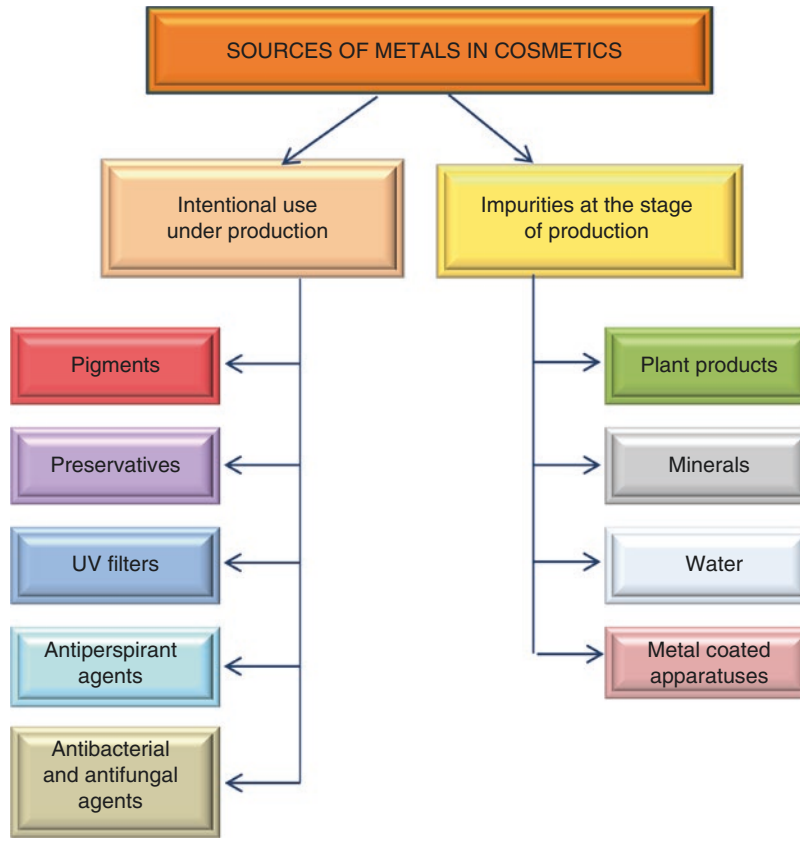

Fig. 15.1 Sources of metals present in cosmetics [4]

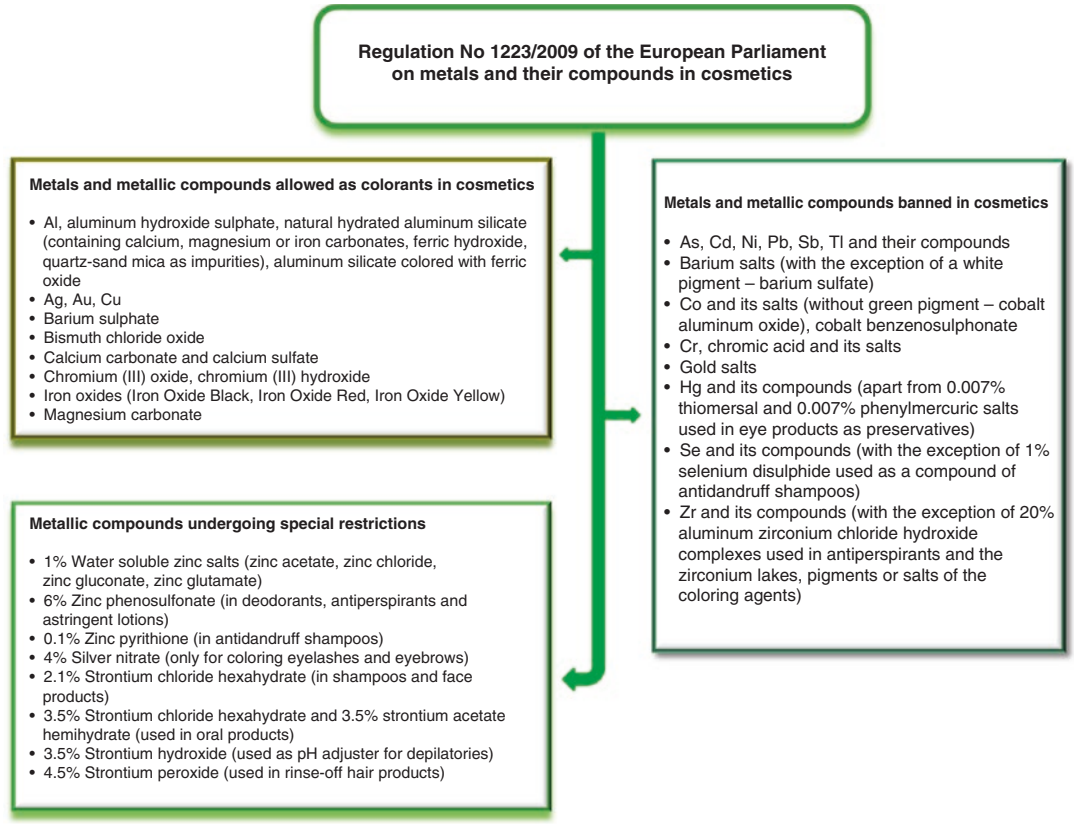

Fig. 15.2 The Regulation No. 1223/2009 of the European Parliament on metals and their compounds in cosmetics [4]

regulatory laws in a given country (Fig. 15.2) [1–4, 23–28].

The other major category of metals in cosmetics are unintended impurities resulting from the use of raw materials (plants and minerals) and water contaminated with metals, as well as from the use of metal-coated apparatuses during cosmetics production. Undesired constituents that may easily enter cosmetics at various stages of production include mainly lead, cadmium, aluminum, mercury, and arsenic. Owing to the ubiquitous presence of numerous metals in the soil, water, and air, some of these are also present in natural ingredients of cosmetics, including especially plants and minerals, and thus traces of numerous metals are unavoidable as impurities in cosmetics containing natural components (Tables 15.1 and 15.2) [45]. In fact, the largest source of metal impurities in cosmetics is the use of natural ingredients in cosmetics production (Table 15.1) [45]. It is important to underline that the same metal may be present in a cosmetic product due to its intentional use and as an impurity [5, 59].

15.3 Legislation on the Presence of Metals in Cosmetics

The presence of metals in cosmetics is prohibited or restricted by regulations in some countries. However, permissible levels of particular metals are individually specified and differ depending on the country and type of product [1–4, 60].

In the EU, the content of metals in cosmetics is strictly regulated by Regulation No. 1223/2009 of the European Parliament [4]. Some metals and their compounds are prohibited for use in cosmetics (lead, cadmium, arsenic, antimony, nickel, thallium, and beryllium), whereas others are restricted (Fig. 15.2). The presence of traditional

Table 15.1 Concentrations of metals in natural components of cosmetics (μg/g)

Metal	Muds[a]	Herbs[b]	Honey	Essential oils[c]	References
Al	18,000–31,000				[29]
As	2.7–15.8	0.08–0.12	ND–0.01		[29–32]
Cd	0.4–1.0	ND–0.63	ND–0.27	0.002–0.02	[29–31, 33–37]
Co	5.7–6.4	0.32–2.35	ND–0.03		[29, 33, 37, 38]
Cr	23–160	1.01–8.71	ND–0.01		[29, 33, 37–40]
Cu	7.1–63	5.6–15.2	0.01–41.27	0.02–0.36	[29, 31–33, 35–38, 41, 42]
Fe	502.7–3,456		1.12–12.9		[33, 37, 38]
Hg		ND–0.17	ND–0.31		[31, 34]
Ni	15–78	1.8–13.1	ND–0.13		[29, 33, 37, 38, 41]
Pb	3.2–35	ND–4,249.6	ND–1.53	0.08–0.17	[29–38, 41]
Zn	22–95				[29, 32, 41]

ND non-detectable
[a]Dead Sea mud, peloid mud from Morinje Bay (eastern Adriatic coast), healing mud from Makirina Bay (central Adriatic)
[b]Horsetail, nettle, chamomile
[c]Lemon, mandarin, bergamot, sweet orange

Table 15.2 Concentrations of metals in cosmetics considered to be natural products (μg/g)

Metal	Kohl	Henna	Commercial muds from Dead Sea and mud-based cosmetics[a]	Cosmetic clays	Herbal products[b]	Black soap	Talcum	References
Al	56.75–1,009	ND–8,803	ND–8,500		126–5,505			[14, 16, 29, 43–45]
As	0.04–1,630	ND–3.927	0.03–1.8		0.690–3.683			[29, 44–47]
Cd	ND–158.6	ND–3.50	ND–2.6	ND–0.53	0.625–21.42	5.69	ND–8.1	[7, 16, 20, 29, 43–46, 48–53]
Co	0.01–10.19	ND–3.54	ND–4.5				ND–2.4	[7, 14, 16, 29, 44, 49, 53, 54]
Cr	ND–8.57	ND–26.07	0.8–30	5.75–7.69	0.15–2.16	0.9 ± 0.07	ND–30	[7, 16, 29, 43, 44, 49, 51–53, 55]
Cu	0–7,581	ND–119	ND–10		2.8–49.1			[7, 14, 16, 20, 29, 43–45, 56]
Fe	60–1,650							[7, 14]
Hg	42.63–67.42	ND–2.4			0–2.183			[16, 45, 46]
Ni	ND–1,140	ND–223	0.01–17		1.04–24.03	5.94 ± 0.39		[7, 14, 16, 29, 43, 44, 47, 52–54, 56]
Pb	ND–277,300	ND–70.11	0.02–6.2	5.13–171.14	0–54.9	1.42	0.24–41	[3, 7, 14, 16, 17, 19, 20, 29, 43–47, 49, 50–52, 55, 56, 58]
Ti	1.7–28,519							[14]
Zn	0.04–284,634	ND–996	0.4–27	2.3–251.6	4.8–56.6			[7, 14, 16, 19, 20, 29, 43–45, 51, 53, 56]

ND non-detectable
[a]Body lotions, hand creams, facial masks, soaps, shaving soaps, shampoos, moisturizers
[b]Creams, toothpastes, various Indian herbal cosmetic preparations

allergens (nickel, chromium, and cobalt) in cosmetics in the EU is strictly regulated [4]. Unlike nickel, which is completely forbidden, cobalt and chromium are prohibited with exceptions. The only allowed cobalt compound is cobalt aluminum oxide, used as a green pigment. Some chromium (III) compounds (chromium (III) oxide, chromium (III) hydroxide) are allowed as colorants in cosmetics, whereas chromium (VI) compounds are banned [4].

Countries such as Algeria, China, India, Israel, Morocco, and Saudi Arabia have reproduced the EU list of regulated cosmetics ingredients [5], whereas the Association of Southeast Asian Nations, El Mercado Comun del Sur of South America, and the Comunidad Andina regions have drafted their own cosmetics regulations using the EU regulations [23–25]. In New Zealand, all heavy metals are prohibited for use in cosmetics [2]. In the USA and Canada, less stringent requirements have been accepted. According to the Food and Drug Administration (FDA), the only banned toxic metal is mercury (with the exception of its use in the form of organic compounds as a preservative in eye cosmetics), and the maximum allowed concentration of lead in cosmetic color additives has been established as 10 μg/g [27]. In South Korea, the limitations depend on the kind of product and are as follows: the lead concentration in makeup products (including eye makeup preparations) and hair preparations (such as shampoos, rinses, and hair sprays) cannot exceed 20 μg/g, and the arsenic level in makeup preparations and hair cosmetics (shampoos, rinses, and hair sprays) should not exceed 10 μg/g and 5 μg/g, respectively, whereas the mercury concentration in basic skin care preparations and baby care cosmetics cannot be higher than 1 μg/g [5, 60]. In Japan, cadmium, mercury, selenium, and strontium and their compounds are prohibited in cosmetics [3].

It is important to underline that the Regulation No. 1223/2009/CE allows the presence in the final cosmetic product of small, technically unavoidable quantities of metals prohibited for use in cosmetics production (referred to as "technically unavoidable traces"), but only if principles of good manufacturing are maintained and the cosmetic deemed safe for the consumer [4]. Unfortunately, permissible levels of metals allowed as "technically unavoidable traces" have not been regulated by the EU, so far. Nonetheless, in order to provide a level of safety for cosmetics users, some countries have established concentration limits as to what may be recognized as technically unavoidable. In Germany, the maximum concentrations of metals in cosmetics recognized as impurities are 1 μg/g for mercury, 5 μg/g for arsenic and cadmium, 10 μg/g for antimony, and 20 μg/g for lead [1], whereas in Canada the values are 3 μg/g for arsenic, cadmium, and mercury, 5 μg/g for antimony, and 10 μg/g for lead [61]. According to the FDA, the limits of metal concentrations in cosmetic raw materials depend on each additive and its color [26–28]. In Brazil, cadmium, chromium, arsenic, and lead are prohibited for use in the manufacturing of cosmetics, and the maximum levels of impurity for metals in organic colorants are 500 μg/g for barium, 3 μg/g for arsenic, 20 μg/g for lead, and 100 μg/g for other metals [62, 63].

Because of growing epidemiological evidence that numerous metals represent a threat to health even with low exposure, nowadays increasing interest has been focused on the question of whether even metal levels recognized as "technically unavoidable" impurities are safe for consumers [5, 64, 65].

15.4 Metals Used in Cosmetic Production

First and foremost, metals have been used in cosmetics as pigments, and their use for this purpose is strictly regulated by the EU (Fig. 15.2) [4]. These metals include mainly chromium, iron, and aluminum compounds, as well as nanoparticles of titanium dioxide (TiO_2), zinc oxide (ZnO), aluminum (III) oxide (Al_2O_3), silver, gold, platinum, and copper [4, 66, 67]. Inorganic metal compounds are used as dyes in eye cosmetics (chromium, titanium, iron), as well as paints and hair coloring shampoos (silver, copper, iron, cobalt, bismuth). Chromium oxide green (Cr_2O_3;

CI 77288) and chromium hydroxide green ($Cr_2O(OH)_4$; CI 77289) are used as colorants in eye shadows [54], which is approved by EU regulations [4]. Moreover, in cosmetics which do not come in contact with the mucous membranes, organic chromium complex (Acid Red 195) may be used. Black iron oxide (Fe_3O_4; CI 77499), yellow iron oxide ($Fe(OH)_3$; CI 77492), and red iron oxide (Fe_2O_3; CI 77491) are also used in eye cosmetics.

Compounds of some essential metals (zinc, copper, iron, and chromium) may also be added to cosmetics during production in order to enhance quality; however, if they are present in excessive amounts, they may be a cause of skin irritation and other adverse effects [5].

Titanium dioxide and zinc oxide nanoparticles and barium sulfate are used as physical UV filters in personal skin care products [68, 69]. Mercury compounds such as thiomersal (thimerosal, sodium salt of ethylmercury thiosalicylic acid) and volpar (phenyl mercuric acetate) are allowed in the concentration of 0.007% in the EU and India and 0.0065% in the USA as preservatives in eye makeup products [4]. Because of the ability of mercury to inactivate tyrosinase (the key melanin-forming enzyme), in some countries metallic mercury, mercury (II) chloride ($HgCl_2$; calomel), and mercury (II) amidochloride are used in skin-lightening creams; thus, the highest concentrations of this element are found in this type of cosmetic [70–74].

Aluminum compounds, apart from their use as colorants, are also used in antiperspirants (Fig. 15.2) [64]. Because aluminum blocks the sweat glands, most antiperspirants contain its compounds such as aluminum (III) chloride, aluminum hydroxy- and dihydroxychloride (aluminum chlorohydrate), aluminum chloride-hydroxide, aluminum-zirconium tetrachlorohydrex gly, and aluminum phenosulfate. Moreover, due to astringent properties (precipitation of blood proteins) allowing inhibition of microvascular bleeding, aluminum compounds are used in aftershave preparations, other astringent face lotions, bath salts, and mouthwashes.

Nowadays a growing use of nanosized silver, gold, platinum, and copper in the cosmetic industry has been noted [66, 67]. Nanoparticles of silver and copper, because of their biological activity, can replace synthetic preservatives used in cosmetics. They can also be added to products for oral hygiene to prevent inflammation of the gums [67]. However, there is still inadequate information on the risks associated with nanometals in cosmetics [66, 67].

15.5 Metals Occurring in Cosmetics as Impurities

A group of cosmetics especially prone to pollution by metals are natural cosmetics and products containing natural ingredients. Due to the ubiquitous presence of metals in natural products, their traces in cosmetic products containing natural ingredients are unavoidable (Tables 15.1 and 15.2). The popularity of natural cosmetics has been increasing in recent years; however, available data show that these products may contain toxic metals in amounts sometimes markedly exceeding acceptable values (Table 15.2) [40]. Concentrations of various metals in the most common natural ingredients in cosmetics, such as essential oils and other ingredients derived from plant sources (i.e., herbal plants, cottonseed oils), sea muds, and honey, are presented in Table 15.1.

Mineral pigments are used in the production of color cosmetics, and impurities of the pigment formulation may result in product contamination with lead, cadmium, chromium, cobalt, copper, nickel, and other elements (Tables 15.3, 15.4, and 15.5) [5, 40, 54]. An example of this is the presence of chromium (VI), which is prohibited in cosmetics in the EU, in allowed colorants such as chromium (III) oxide and chromium (III) hydroxide. High quantities of chromium (VI) have been detected in eye shadows and henna (Tables 15.2 and 15.4) [5].

It is important to underline that the high sensitivity of currently available analytical methods for metal analysis in cosmetics enables the detection of even trace concentrations [14, 55, 77, 84, 86, 90, 113, 119]. Thus metals can be detected as trace impurities in most cosmetics present on the

Table 15.3 Concentrations of arsenic, cadmium, mercury, and lead in cosmetics (μg/g)

Metal	Color cosmetics	Face and body care products	Hair cosmetics	References
As	ND–11.1	ND–15.4	0.16–0.81	[14, 43, 46, 72, 75–81]
Cd	ND–1,066	ND–16.5	ND–2.47	[7, 12–15, 17, 18, 43, 44, 46, 50, 52, 53, 57, 65, 72, 75–80, 82–100]
Hg	ND–90.3	ND–65,133	0.01–90.32	[46, 70–73, 75–78, 82, 88, 101]
Pb	ND–10,185	ND–693	ND–29.68	[7, 12–15, 17–19, 39, 44, 46, 50, 52, 53, 57, 65, 72, 75–84, 86–92, 94–104, 110, 111]

ND non-detectable

Table 15.4 Concentrations of metals in eye cosmetics (μg/g)

Metal	Eye shadows	Mascara	Eyeliners/eye pencils	References
Al	806–50,000	ND–289,000	130–4,779	[14, 43, 44, 75]
Co	ND–303.7	0.15–103	0.002–28.160	[14, 17, 44, 52, 53, 75, 77, 78, 100, 112–114]
Cr	ND–149,500	ND–21.3	ND–64.3	[14, 17, 44, 52–54, 75, 77, 78, 81, 89, 100, 107, 112, 113]
Cu	ND–424.9	ND–325.2	ND–178	[14, 17, 43, 44, 75, 77, 83, 115]
Fe	2.2–160,000	52.5–106,745.5	ND–217,691	[14, 17, 75, 89, 107, 115, 116]
Ni	ND–4,148	0.05–588.5	ND–69	[14, 17, 43, 44, 52, 53, 75, 77, 78, 81, 83, 89, 98, 100, 107, 108, 112, 113]
Sn	46.5–6,114.5	19.3–25.6		[14, 75]
Ti	4.13–7.96	4.7–354.1	2.03–68.51	[14]
Zn	0.02–20,000	ND–236,159	8.02–2,095.41	[14, 17, 19, 43, 44, 53, 75, 89, 98, 107, 115]

ND non-detectable

Table 15.5 Concentrations of metals in other cosmetics (μg/g)

Metal	Color lip cosmetics (lipsticks, lip glosses)	Nail polishes	Foundation creams, powders, compact powders, face paints, blushes, white powder, red powders	Tattoo inks	References
Al	7.7–27,032	ND–13,600	ND–18,661.5	ND–878	[14, 43, 44, 82, 92, 94, 106]
Co	ND–26.5	ND–8.6	ND–15.2	0.05–2.25	[7, 13–15, 17, 43, 44, 53, 77, 78, 86, 87, 92, 94, 106, 114, 117]
Cr	ND–115.8	ND–8.25	ND–15,000	8–27	[7, 12, 13–15, 17, 43, 44, 52, 53, 77–80, 86, 87, 89, 90, 92, 94, 113, 117, 118]
Cu	ND–254.5	ND–590	ND–49.1	2.25–2,480	[7, 14, 15, 17, 43, 44, 77, 86, 87, 92, 94, 106, 115]
Fe	ND–44,070	ND–17,900	ND–261,276	69.8–454	[7, 14, 17, 89, 92, 106, 114, 115, 117]
Ni	ND–344	1.9–56.2	ND–214.5	0.6–8.4	[7, 14, 15, 17, 43, 44, 52, 53, 77–80, 86, 87, 89, 92, 94, 98, 106, 108, 113]
Ti	ND–16,322.2		0.69–28,519		[14, 94]
Zn	ND–3,810	ND–595	ND–112,000	31.5–138	[7, 14, 17, 19, 43, 44, 53, 89, 92, 98, 106, 115, 117]

ND non-detectable

market, even when these products are manufactured in adherence with good practice [12, 18, 20]. Taking into account available epidemiological data indicating that even low exposure to some metals may be unfavorable for health, along with the possibility of dermal and sometimes also gastrointestinal and inhalational absorption of metals present in cosmetics, it has been recommended to minimize cosmetics contamination with metals [64].

15.6 Levels of Metals in Cosmetics

Because of growing interest in cosmetics as a potential source of adverse exposure to metals, there has been increasing data on metal concentrations in cosmetics in recent years (Tables 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8); however, due to a lack of regulations in some countries, the data are still limited to only certain groups of products. Eye cosmetics are mainly analyzed for nickel, cobalt, and chromium, lipstick for lead, skin creams for mercury, and natural cosmetics for lead, cadmium, arsenic, mercury, nickel, cobalt, and aluminum (Tables 15.2, 15.3, and 15.4) [20, 42, 51, 53].

In Tables 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8, concentrations of metals which have been recognized as allergenic (nickel, chromium, cobalt, iron, aluminum, beryllium, copper, gold, palladium, titanium, platinum, tin, and zinc) and nonallergenic (cadmium, lead, mercury, and arsenic) in various categories of cosmetics (color cosmetics, face and body care products, hygienic products, hair cosmetics, and cosmetics recognized to be natural products) are presented based on the available data. As can be seen in Tables 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8, concentrations of these metals in many cosmetics on the market are below metal impurity limits and often also below the limit of detection; thus, using these products does not present potential risk to their users [18, 53, 77, 83]. On the other hand, there are also data indicating that concentrations of metals in various cosmetics are excessively high (Tables 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8) [14, 16, 17, 43, 44, 52, 75, 81, 89, 98, 100, 107, 108, 112, 113]. With regard to metal allergens, an important problem is the presence of excessive levels of nickel, cobalt, and chromium in color cosmetics, especially in eye products such as eye shadows, mascaras, eyeliners, and eye pencils (Tables 15.4 and 15.5).

Table 15.6 Concentrations of metals in face and body care products (μg/g)

Metal	Face care products[a]	Body care products[b]	Other cosmetics[c]	References
Al	ND–1,217	ND–688	ND–158	[14, 18, 43, 44, 72]
Al		ND–1.002 (μg/ml)		[120]
Co	ND–4.61	0.011–0.036	0.013–0.073	[7, 14, 18, 44, 72, 88, 99]
Cr	ND–27.07	0.022–4.364	0.027–0.891	[14, 18, 43, 44, 52, 72, 85, 88, 89, 118]
Cr		ND–0.097 (μg/ml)		[120, 121]
Cu	ND–65.34	2.97–8.46	0.57–7.57	[7, 14, 18, 43, 44, 72, 85, 99]
Fe	ND–2,469			[7, 14, 18, 89, 103]
Fe		0.05–1.83 (μg/ml)		[120]
Ni	ND–27.50	ND–6.56	0.104–0.191	[7, 14, 18, 43, 44, 52, 72, 88, 89, 98, 99, 103, 108, 121]
Ti	2.5–5,515.4			[14, 76]
Zn	ND–996		0.136–1.104	[7, 14, 18, 43, 44, 85, 89, 98]

ND non-detectable

[a]Cleansing oils, treatment masks, treatment essences, essences UV, whitening daily scrubs, skin-lightening creams, non-skin-lightening creams, facial creams, oil-free makeup removers, face cleansers, anti-freckle creams, moisturizing creams

[b]Shower gels, body care lotions, shaving creams, hand and cuticle creams, body creams, emulsions, skin-lightening body milks, foam bath products

[c]Beauty creams, skin creams, smoothing and hydrating creams, medicated creams, non-medicated creams

Table 15.7 Concentrations of metals in hair products (μg/g)

Metal	Shampoos	Conditioners[a]	Hair styling products[b]	Hair dyes	References
Al	65.10–106.98	25.58–70.86	91.75–192.41	ND–120	[14, 72]
Co	0.01–0.37	0.03–0.05	0.03–16.04	ND–4.5	[7, 14, 72, 84, 106]
Cr	0.34–1.15	ND–1.12	0.06–1.75	ND–11	[7, 14, 72, 85, 97, 106, 119]
Cu	0.07–5.06	0.52–4.69	0.57–22.77	ND–10.8	[7, 14, 72, 84, 85, 91, 97, 106]
Fe	28–154	0.51–2.15	0.76–209.87	ND–331	[7, 14, 84, 85, 91, 97, 106]
Ni	0.07–3.11	0.01–2.03	0.02–11.27	ND–43.5	[7, 14, 52, 72, 84, 85, 97, 106]
Ti				117–868	[14]
Zn	0.5–1,500	0.53–0.81	0.65–17.55	ND–298	[7, 14, 84, 85, 97, 106]

ND non-detectable
[a]Hair creams, medicated hair creams, hair conditioners, hair treatment creams, anti-dandruff creams, hair food formulas
[b]Hair relaxers, hair styling creams and gels, hair pomades

Table 15.8 Concentrations of metals in hygienic products (μg/g)

Metal	Antiperspirants and deodorants	Soaps[a]	Toothpastes, mouth cleansing powders	References
Al	69–183,500	86–1,224	224–1,436	[72]
Co	ND–2.8	0.003–0.018	0.02–2.61	[72, 88]
Cr	ND–25	ND–1.11	0.01–6.29	[52, 72, 85, 88, 97]
Cu	2.0–6.4	0.10–22.22	0.1–22.99	[72, 85, 97]
Fe	4.7–91.2	0.45–1.58	0.5–0.7	[85, 97]
Ni	ND–4.9	ND–7.17	0.01–29.39	[52, 65, 72, 85, 88, 97, 108]
Zn	78–132	0.2–1.1	0.11–0.41	[85, 97]

ND non-detectable
[a]Handwashes, beauty soaps, cream soaps, germ shield soaps, cleaning bars, toilet soaps, medicated and non-medicated soaps, skin-lightening and non-skin-lightening soaps

15.7 Factors Affecting Metal Exposure in Cosmetics

Consumers use on average several cosmetics every day during their lifetimes. Thus, even if metals are present in cosmetics at very low concentrations, repeated use of these products may result in significant cumulative exposure to sometimes numerous metals. It is also important to underline that metal-containing cosmetics constitute a source of occupational exposure for hairdressers and beauticians [122–124].

Various scenarios of exposure to metals present in cosmetics are possible (Fig. 15.3). Cosmetic products may result in brief contact such as with rinse-off products (e.g., shampoos, shower gels, toothpastes) or remain in contact with the skin over long hours such as with leave-on products (e.g., face creams, body lotions, lipsticks). Preparations may be applied to a large body surface area. Increased absorption may occur when cosmetics come into contact with thin-skinned areas such as the eyelids, conjunctiva, or genital regions, as well as the skin of children, in whom absorption via the skin is higher than in adults. Local factors such as tears and sweat may also increase absorption. In the case of metals present in lipsticks, there is a risk of oral ingestion, whereas ingredients of the products applied in the form of sprays may be absorbed via inhalation (Fig. 15.3).

It is important to underline that metal exposure in cosmetics depends on numerous exogenous and endogenous factors that determine skin permeability to them [125, 126]. The former group involves factors such as dose and physicochemical properties of the metal and its vehicle (molecular volume, counterion, nature of chemical bond, polarity, valence, protein reactivity, tissue deposition, solubility, and pH), as well as duration of exposure [126]. The second group involves anatomical site, age of the skin, as well

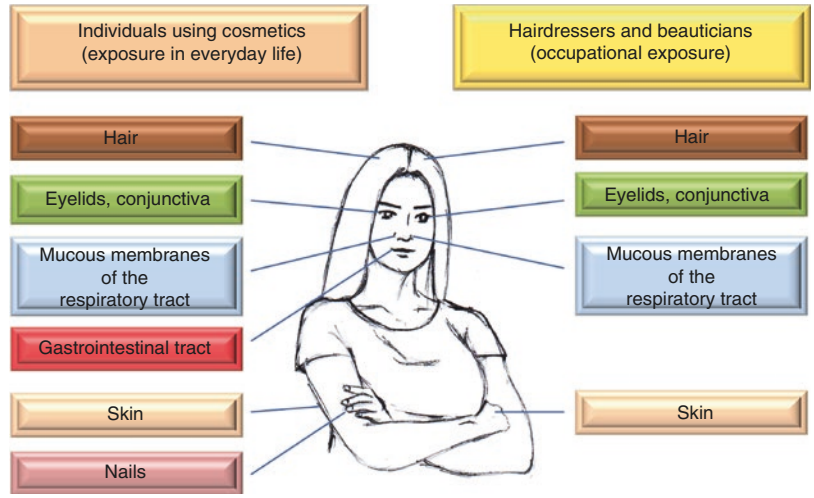

Fig. 15.3 Possible sites of exposure to metals present in cosmetics

as health status of the skin and skin appendages [126]. It is important to underline that the predisposing factors to the absorption of metals via the skin may be stratum corneum disruption due to occupational exposure to chemicals and occurrence of occupational skin diseases [125, 127]. One of the important factors capable of influencing skin permeability is propylene glycol, which increases metal penetration via the skin [125].

Studies conducted by Ross-Hansen et al. [128] and Thyssen et al. [129] suggest that individuals with filaggrin gene null mutations are predisposed to contact sensitization to nickel [128, 129]. Filaggrin is a filament-associated protein that binds to keratin fibers in epithelial cells and is essential for the regulation of epidermal homeostasis. Histidine-rich filaggrin proteins in the epidermis chelate ions of nickel and, in this way, prevent penetration via the skin and subsequent systemic exposure to this toxic metal. Thus, filaggrin gene null mutations may be a risk factor for the development of sensitization to nickel [128, 129].

15.8 Consequences of the Presence of Metals in Cosmetics

Metals present in cosmetics may penetrate human skin and sometimes may also be absorbed via mucous membranes, the respiratory tract, and the gastrointestinal tract, producing various unfavorable effects via individual and occupational use (Figs. 15.3, 15.4, and 15.5).

Elements present in cosmetics applied topically may accumulate in the skin or be absorbed into the general circulation. Metals such as nickel, chromium, cobalt, and selenium mainly accumulate in the stratum corneum and may cause cutaneous effects (e.g., allergic contact dermatitis). Soluble and diffusible nickel compounds are capable of penetrating the stratum corneum via the skin appendages (hair follicles, sweat glands, and sebaceous glands), as well as via transcellular or intracellular pathways, but the penetration of this metal across the stratum corneum is slow and approaches only 1% of the amount applied to the skin [5]. However, it should be taken into account that nickel absorption may be changed by factors influencing the skin's permeability [126]. At the epidermal level, metal, being a hapten, binds to amino acid residues of proteins, forming metal-protein complexes capable of causing contact allergy [130]. Allergic reactions are the most common cutaneous adverse effect of metals present in cosmetics, and nickel is the most important metal allergen in these products [5, 6, 22].

Reported cases of allergy due to metals present in cosmetics have been caused mainly by color cosmetics containing nickel, cobalt, and chromium [8–11, 39, 125, 131, 132]. Although some

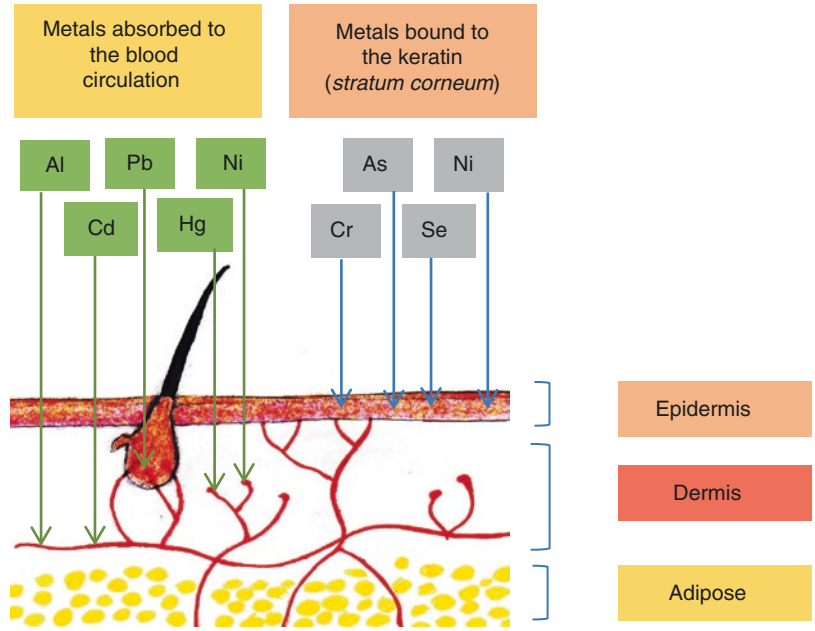

Fig. 15.4 Schematic representation of metal accumulation in the skin and absorption through the skin

other metals have also been recognized to be capable of inducing allergic reactions, in the available literature, we have found no reported cases of allergy caused by the presence of these metals in cosmetics, except for iron [125, 133, 134]; however, their contribution to the development of allergic reactions cannot be excluded. It is also important to underline that due to the simultaneous presence of numerous allergens in cosmetics, it may be very difficult to identify all ingredients of the product resulting in positive allergic reactions. Of note, a cross-sectional population study conducted by Thyssen et al. [135] revealed no association between nickel allergy and self-reported cosmetic dermatitis from eye shadow and mascara.

Metal allergen-containing eye makeup is especially dangerous because these products are applied directly to the delicate skin of the eyelids which is characterized by a very thin stratum corneum, making percutaneous absorption of metals very easy. Metals present in eye cosmetics may also penetrate via the conjunctiva. Moreover, tears and sweat increase their absorption at the periocular area. Owing to the particular susceptibility of the eyelid skin, metal allergens (particularly nickel) may cause elicitation of allergic contact dermatitis even at very low concentrations, especially under repeated application [10, 11].

It has been recommended that the nickel concentration in household products should not exceed 5 μg/g and that to minimize the risk of allergic reactions in sensitized persons, the concentrations of nickel, cobalt, and chromium in cosmetics should preferably be below 1 μg/g [21]. This is not always the case (Tables 15.2–15.8). Sipahi et al. [136] have reported that concentrations exceeding 1 μg/g were detected in 97%, 96%, and 54% of products with regard to nickel, chromium, and cobalt, respectively. Examined products among the most commonly used cosmetics included mascaras, eyeliners, eye shadows, lipsticks, and nail polishes. After calculation of the systemic exposure dosage (SED) of these metals, risk was assessed to be negligible; however, it is likely that contact dermatitis may result from exposure to the reported levels of metal allergens in at least some sensitized individuals.

Occupational dermatitis has been reported in hairdressers and beauticians [122–124]. Relevant

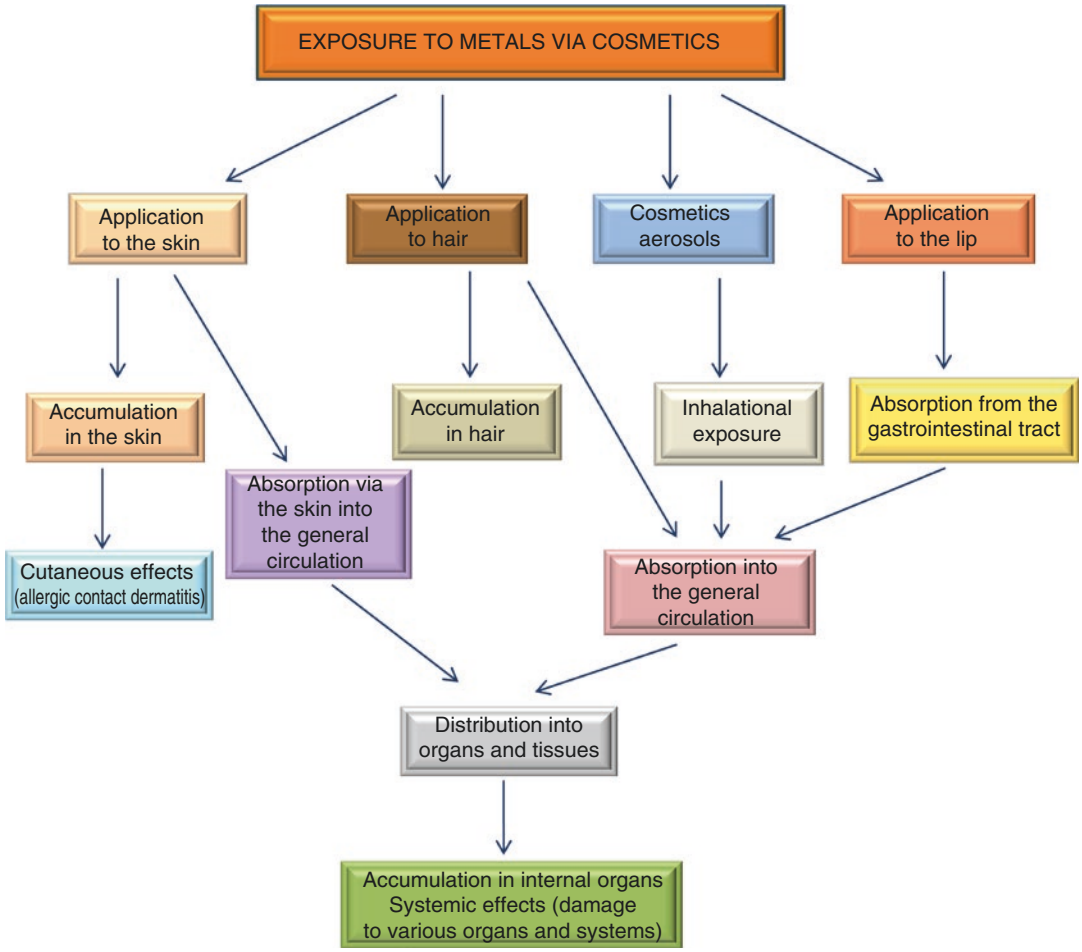

Fig. 15.5 Possible consequences of exposure to metals via cosmetics

allergens and irritants include, apart from organic compounds (glyceryl thioglycolate, p-phenylenediamine, 2-hydroxyethyl methacrylate, and quaternium-15), nickel sulfate found in cosmetic products [124]. Occupational dermatitis may develop after a relatively short time [123].

Metals (e.g., mercury, cadmium, lead, aluminum, and nickel) able to penetrate the skin may be absorbed systemically and transported to various organs (Figs. 15.4 and 15.5). With repeated exposure, they may accumulate and cause damage to the internal organs, resulting in neurological disorders; cardiovascular problems; liver, kidney, and lung damage; reproductive and developmental disorders; and malignancy (Fig. 15.5) [48, 101, 137–145].

15.8.1 Reported Cases of Allergic Reactions to Metals in Cosmetics

In the available literature, some cases of well-documented allergic reactions due to metals present in cosmetics have been reported. The most common culprits have been eye makeup products such as pencils, eye shadows, and mascaras containing nickel, cobalt, or chromium [8–11, 39, 125, 131, 132]. It is important to emphasize that two or more metal allergens may be present in the same cosmetic product, especially in color cosmetics, increasing the risk of allergy [8, 59, 132]. Individuals allergic to nickel are often allergic to cobalt as well, and concomitant sensitization to

the two metals appears to enhance the severity of the allergic reaction [146]. Bonefeld et al. [147] proposed that nickel acts as an adjuvant during cobalt sensitization. They revealed, using a mouse model, that the presence of nickel during cobalt sensitization potentiated the immune response to cobalt more than the presence of cobalt during nickel sensitization influenced the immune response to nickel. Other culprits have included foundations, henna, nail polishes, and a massage cream [59, 125, 148, 149]. Of note, allergic reactions were reported even when using cosmetics containing nickel in amounts significantly lower than the proposed limit value (1 μg/g) [10, 11, 125].

Allergic contact dermatitis of both eyelids was noted in a 47-year-old nonatopic woman who had used a green eye pencil containing 0.028 μg Ni/g [10]. Symptoms lasted 4 months and disappeared after discontinuation of the product and returned after reinitiation. Patch tests showed positive reactions to nickel and the green pencil. Moreover, the woman was allergic to imitation jewelry. Allergic eyelid dermatitis was also reported in two young Dutch women (22 and 18 years old) who had used eye shadows containing nickel at the concentrations of 76 and 87 μg/g. Moreover, one of them had a history of previous dermatitis after use of a mascara which contained 102 μg Ni/g [135]. Verhulst et al. [11] reported a case of palpebral eczematous dermatitis in a 47-year-old nonatopic woman caused by the use of a blue-gray eye pencil containing 0.015 μg Ni/g in the blue part of the pencil and 0.029 μg Ni/g in the gray. When the woman replaced the pencil with a different brand product, improvement occurred. Patch tests revealed positive reactions to nickel, palladium, and the two colored parts of the eye pencil. Because no palladium was detected in both parts of the pencil, the changes were deemed to be caused by nickel. Karlberg et al. [39] reported eyelid dermatitis in persons with contact allergy to nickel due to this metal's presence in mascara. Eyelid eczema, lasting 13 months, was also noted in a 30-year-old Georgian woman who used an eye pencil containing 1.4 μg Ni/g and 6.19 μg Cr/g [132]. The eczema disappeared as a result of treatment with corticosteroids but returned when the pencil was used again. Patch tests revealed allergy to nickel, chromium, and cobalt. The threshold for allergic activity to chromium (VI) is 5 μg/ml [54].

Goh et al. [8] presented a case of a 21-year-old Chinese woman who suffered from edema and eczema of her eyelids due to the use of eye shadow containing 15.9 μg Ni/g and 4.5 μg Co/g. Symptoms resolved with discontinuation. Previously, the patient had suffered from the same symptoms after using an eye shadow of another brand, and she had a history of allergy to imitation jewelry. Patch testing revealed positive reactions to nickel and cobalt.

Foulds [125] reported five cases of facial eczema in nickel-sensitive females due to the use of foundation containing iron oxide pigments (CI 77492, CI 77489, CI 77499, and CI 77491), with trace amounts of nickel as an impurity. Even with trace amounts of nickel (below the concentration expected to elicit an allergic reaction), an allergic reaction was elicited in a nickel-sensitized individual when combined with propylene glycol, which enhanced metal penetration. Irritation and persistent allergic contact dermatitis of the eyelids and periocular region (lasting 10 months) were noticed in a 44-year-old English woman who used mascara containing 5% black iron oxide [133]. After discontinuation, her condition improved. Patch testing to the mascara ingredients (provided by the manufacturer) revealed a strong allergic reaction only to 5% black iron oxide. Zugerman [134] reported a case of a 43-year-old nonatopic white woman suffering from bilateral upper and lower eyelid erythema caused by yellow iron oxide present as a dye in her mascara (which she reacted to on patch testing). However, it needs to be underlined that iron oxide in cosmetics is a rare cause of eyelid allergic contact dermatitis. In the available literature, we have found only the two above presented cases [133, 134].

Guarneri et al. [149] reported the case of a woman suffering from cobalt-induced allergic contact dermatitis due to a nail-art procedure performed by a beautician. Moreover, the woman repeated the procedure at home with a nail gel that contained cobalt. She developed intensely pruritic eczematous periungual and palmar lesions on

both hands. Severe hand eczema was noted in a therapist as a result of the presence of cobalt in a cream used for facial massage under iontophoresis [148]. Kang and Lee [59] reported a case of allergic contact dermatitis after use of henna, which may have been in reaction to nickel (2.5–3.96 μg/g) and cobalt (2.96–3.54 μg/g), as well as *p*-phenylenediamine present in this product. It is important to underline that in most of the above described cases of allergy to cosmetics, positive reactions to metals were determined via patch tests [8, 10, 11, 131, 132].

It has been reported that titanium dioxide present in cosmetics induces eyelid dermatitis in patients allergic to gold [150]. This compound adsorbs gold released from jewelry and in this way can induce allergic contact dermatitis to gold despite the absence of gold in eye cosmetics [150].

Occupational allergic contact dermatitis due to nickel and cobalt present in cosmetics has been noted in hairdressers and beauticians [122–124]. Matsunaga el al. [123] noticed the onset of allergic contact dermatitis in beauticians or those in training within 1 month to 1 year of their starting this occupation, due to the use of hair dyes, shampoos, and cold permanent wave primary solutions. Positive patch test reactions were also noted to, among others, nickel sulfate, cobalt sulfate, and thiomersal [123]. Zhao and Li [151] investigated the prevalence of sensitization among university student volunteers in Beijing and noted that thimerosal was the leading allergen (19.4%) and that the rate of positive patch tests in women (23.6%) was significantly higher than in men (9.8%).

15.8.2 Other Effects

Other effects caused by both allergenic and non-allergenic metals may occur [5, 6, 140, 143]. Strong toxic effects in the form of internal organ damage have been noted as a result of the presence in cosmetics of cadmium, lead, mercury, and aluminum [48, 101, 137–145]. Some cases of poisonings due to the use of skin creams, mainly lightening preparations containing mercury, have been reported [140, 142–145]. In spite of the commonly known high toxicity of mercury, creams containing this element are still used in many developing countries. Lower back pain [101], ankle swelling [144], sleep disorders and kidney damage with proteinuria [141, 144, 145] have been reported in the users of skin-lightening creams. Systemic allergic contact dermatitis, erythema, and itchy papulo-vesicular lesions several hours after the application of a skin-lightening cream containing mercury have been observed [142]. It is important to underline that unfavorable effects due to the application of these cosmetics were also noted in family members [138], and particularly dangerous cases of poisonings by mercury from cosmetics have been noted in children and pregnant women [116, 137].

Many cases of poisonings have been found due to lead present in eyeliner (called kohl or surma), which may be absorbed via the conjunctiva or during lacrimation, eye rubbing, and finger sucking by children [48, 139]. Amry et al. [152] reported the case of a 21-year-old Saudi woman suffering from severe corneal edema and faint scarring due to the use of eyeliner contaminated with cadmium.

The presence of aluminum in cosmetics may also be dangerous [153–155]. Guillard et al. [153] reported the case of a 43-year-old woman who suffered from hyperalbuminemia, bone pain, and extreme fatigue as a result of the everyday use for 4 years of an antiperspirant cream containing aluminum chlorohydrate, which was her only source of exposure to this element (daily dose of 0.108 g of aluminum (III), which over a 4-year period amounted to 157.3 g). Under repeated exposure, aluminum accumulates in the brain and bone tissue, contributing to the development of Alzheimer's disease, other neurodegenerative disorders [156], and osteomalacia [153]. It has also been suggested that aluminum in antiperspirants can contribute to the development of breast cancer [154, 157].

Finally, it has been reported that prolonged high exposure to zinc from personal care products can be a cause of hair and nail fragility, gastrointestinal disorders, neurological abnormalities, and convulsions [85].

15.9 Summary

Cosmetics may contain numerous metals, including elements capable of inducing allergic reactions. Reported cases of allergy due to the presence of metals even at low concentrations (below 1 μg/g) suggest that the acceptable levels of metals recognized as "unavoidable impurities" should be defined and efforts should be undertaken to decrease metal release in cosmetics. Patients with history of metal allergy should not use cosmetic products containing metal allergens, especially nickel, chromium, cobalt, or iron, whereas individuals allergic to gold should avoid the use of cosmetics containing titanium dioxide. However, avoidance of these metals is difficult due to their prevalence in many cosmetics and the fact that cosmetic products often lack information regarding metal content on their packaging. In order to fully assess the safety of metal-containing cosmetic products, postmarketing vigilance and monitoring are necessary [136].

Conflict of Interest The authors declare that there are no conflicts of interest.

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Metals in Coins

16

Kelsey E. Hirotsu and Jennifer K. Chen

16.1 Introduction

Historically, the world's first coins were made from precious metals such as gold and silver; however, their intrinsic value led to a shortage that governments could not meet to sustain circulation [1]. Therefore, base metals such as nickel, copper, manganese, zinc, and aluminum were employed to manufacture coins with intrinsic value lower than face value. It was soon noted that the use of alloys permitted the manufacture of coins with particular characteristics: for example, the use of nickel-containing alloys has predominated due to nickel being corrosion resistant, durable, malleable, easy to stamp, and recyclable [2]. Currently, copper-nickel (cupronickel) is the most commonly used alloy worldwide.

16.2 History

The ancient Bactrians are credited with forging the first coins using nickel alloys around 250 B.C. [2, 3]. In 1850, the Swiss were the next to employ nickel in coinage, experimenting with combinations of copper, zinc, and silver to create an ideal alloy. In 1857, the United States began using a nickel alloy for coins, and in 1865 the 3-cent nickel, composed of one part nickel and three parts copper, was introduced [4]. A year later, the 5-cent nickel was introduced in the same copper-nickel alloy. From 1942 to 1946 during World War II, the nickel coin took a brief hiatus from the traditional copper-nickel alloy, as nickel and copper represented key metals used for stainless steel and ammunition casings, respectively; during this period, the nickel coin was a copper, silver, and manganese alloy. Otherwise, the copper-nickel 3-to-1 alloy has persisted and has gained popularity for use in other coins and currencies as well.

Since the twentieth century, copper-nickel has remained the most common alloy in coins [5]; however, in the twenty-first century, the cost of copper and nickel has been rising. Thus, countries such as India have turned to cheaper metals such as aluminum, iron, and chromium to manufacture their coins.

16.3 Coin Metals and Alloys in Current Circulation

All alloys discussed in this chapter and their compositions are listed in Table 16.1. Hamann et al. [5] collected 850 coins of 361 denominations from 52 countries, covering 75% of the world's population, and performed analysis of elemental

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Table 16.1 Summary of coin alloys, platings, composition, and nickel release from coins (Reproduced with permission from [1, 5])

Name of coin alloy and composition of coins[a]	Composition of alloys and platings—metals and concentration (%)	Examples	DMG test positive/ no. coins tested
Acmonital, Italian monetary steel, stainless steel	Fe 81.5; Cr 18.5	50, 100, 500 lire (steel part) (ITL)[b]	0/28
Aluminum	Al 100	1 yen (JPY). 1, 2, 3, 5 paise rupee (INR)	0/17
Aluminum-bronze/aluminum-brass	Cu 92; Al 6; Ni 2	20 krone (DKK), 500 lire (yellow part) (ITL)[b] 10 centime (FRF)[b]	35/62
Bronze and brass	Cu 97; Zn 2.5; Sn 0.5	50 øre (DKK)	0/29
Copper-nickel, cupronickel, CuNi	Cu 75; Ni 25	1, 2 euro (silver-colored part) (EUR). Many other coins worldwide (including GBP, DKK, SEK, USD)	100/100
	Cu 84; Ni 16	20 pence (GBP)	
Manganese-brass	Cu 88.5; Zn 6; Mn 3.5; Ni 2	1 dollar (USD)	
Nickel	Ni 100	1, 2 franc (FRF)[b]	8/8
Nickel-brass	Cu 75; Zn 20; Ni 5	1, 2 euro (yellow part) (EUR), 1 pound (GBP)	39/39
Nordic gold	Cu 89; Al 5; Zn 5; Sn 1	10, 20, 50 cent (EUR), 10 krona (SEK)	0/5
Silver in CuNiZn	Ag 40 in Cu 50; Ni 5; Zn 5	1 krona (SEK)[c]	
Plated, covered	CuNi-plated Cu	10, 25, 50 cent (USD)	1/1
	Cu-plated steel	1, 2, 5 cent (EUR) 1, 2 pence (GBP)	0/18
	Cu-plated Zn	1 cent (USD)	0/5
	Ni-plated steel	5, 10 pence (GBP)[d]	43/43
Combination coins, bicolor, bimetallic	Outer and inner parts of different alloy (two colors)	1, 2 euro (EUR)	
		2 pound (GBP)	
Three layers	A core with a layer of other alloy or metal on each surface	5 krona (SEK), 1, 2 euro (inner part) (EUR)	

[a]Italics = primary expression used; normal font = other often used expression
[b]Replaced by the euro
[c]Manufactured until 1968
[d]Introduced in 2012

composition and nickel release via X-ray fluorescence spectrometry and the dimethylglyoxime (DMG) test, respectively (Tables 16.1 and 16.2). Copper-nickel was found to be the most commonly used alloy worldwide, and aluminum-bronze was the second most common. While all copper-nickel coins tested DMG positive regardless of denomination, approximately half of the aluminum-bronze coins had low or undetectable levels of nickel release upon DMG testing (Tables 16.1 and 16.2). Other coin alloys with negative DMG tests included stainless steel, aluminum, bronze, Nordic gold, and bronze- or copper-plated coins. Conversely, nickel-plated steel and nickel-brass, as expected, tested positively for nickel release on the DMG test (Table 16.2).

Copper-nickel has been abundantly used in denominations of large developed countries, including the US dollar, the euro, the UK pound, the Danish krone, and the Swedish krona [1, 5] (Table 16.3), although in some cases changes to coin composition have been implemented in

Table 16.2 Nickel-releasing coins (DMG test positive), nickel-containing coins (according to XRF) with negative or doubtful DMG test results, and nickel-free coins (determined by XRF, absence of positive DMG), identified among circulating coins in 52 countries (2011–2012) (Reproduced with permission from [5])

	Number of nickel-releasing denominations/issues						
Composition (alloy, coating by plating or clad)	Africa	Asia	Europe	Latin America	North America	Oceana	Total
Aluminum-bronze and aluminum-brass	4	13	3	15	–	–	35
Copper-nickel	18	40	24	10	4	4	100
Nickel	1	–	–	3	4	–	8
Nickel-brass	5	11	8	15	–	–	39
Copper-nickel-plated/clad Cu; Ni; steel	4	–	4	–	3	–	11
Nickel-plated/clad Cu; steel	12	15	2	17	–	–	46
Combination coin alloys—results included above	14	12	8	12	1	–	47
All with positive DMG test result	44	79	41	60	11	4	239
	Number of nickel-containing denominations/issues with negative or doubtful DMG test results						
Composition (alloy, coating by plating or clad)	Africa	Asia	Europe	Latin America	North America	Oceana	Total
Aluminum-bronze	6	6	1	6	1	2	22
Brass and bronze	1	–	–	1	–	–	2
Stainless steel	–	–	–	1	–	–	1
Bronze-plated/clad Ni	–	–	–	–	1	–	1
Copper-plated/clad steel; Zn	–	–	–	3	–	–	3
Combination coin alloys—results included above	6	5	1	2	1	–	15
All nickel-containing with negative or doubtful DMG test results	7	6	1	11	2	2	29
	Number of nickel-free denominations or issues						
Composition (alloy, coating by plating or clad)	Africa	Asia	Europe	Latin America	North America	Oceana	Total
Aluminum	1	12	–	4	–	–	17
Aluminum-bronze	–	2	–	3	–	–	5
Brass and bronze	8	5	5	7	2	–	27
Nordic gold	–	1	4	–	–	–	5
Stainless steel	1	10	–	16	–	–	27
Brass and bronze-plated/clad steel	4	8	2	13	–	–	27
Copper-plated/clad Al; steel; Zn	5	7	5	2	2	–	21
Combination coin alloys—results included above	3	1	1	7	–	–	12
All nickel-free	19	45	16	45	4	0	129

Table 16.3 Metal composition (alloys and platings) of coins in circulation in 2012 in the EU countries that have adopted the euro (euro area), the United Kingdom, Denmark, Sweden, and the United States (Reproduced with permission from [1])

Euro area Euro (EUR)		UK pound sterling (GBP)		Denmark Danish Krone (DDK)		Sweden Swedish Krona (SEK)		US dollar (USD)	
2 euro	Outer silver-colored part: Cu 75; Ni 25 Inner yellow part, three layers: Cu 75; Zn 20; Ni 5, Ni 100, Cu 75; Zn 20; Ni 5	5 pound	Cu 75; Ni 25	20 krone	Cu 92; Al 6; Ni 2	10 krona	Cu 89; Al 5; Zn 5; Sn 1	1 dollar	Cu 88.5; Zn 6; Mn 3.5; Ni 2
1 euro	Outer yellow part: Cu 75; Zn 20; Ni 5 Inner silver-colored part, three layers: Cu 75; Ni 25, Ni 100, Cu 75; Ni 25	2 pound	Outer yellow part: Cu 76; Zn 20; Ni 4 Inner silver-colored part: Cu 75; Ni 25	10 krone		5 krona	Three layers: Cu 75; Ni 25, Ni 100, Cu 75; Ni 25	50 cent (half dollar) 25 cent (quarter) 10 cent (dime)	CuNi-plated Cu
50 cent	Cu 89; Al 5; Zn 5; Sn 1	1 pound	Cu 70; Zn 24.5; Ni 5.5	5 krone	Cu 75; Ni 25	2 krona	Cu 75; Ni 25	5 cent (nickel)	Cu 75; Ni 25
20 cent		50 pence	Cu 75; Ni 25	2 krone		1 krona	Cu 75; Ni 25	1 cent (cent, penny)	Cu-plated Zn
10 cent		20 pence	Cu 84; Ni 16	1 krone					
5 cent	Cu-plated steel	10 pence	Cu 75; Ni 25	50 ore	Cu 97; Zn 2.5; Sn 0.5				
2 cent		5 pence	Ni-plated steel						
1 cent		2 pence	Cu-plated steel						
		1 penny							

recent years (see "Regulatory Efforts" below). The Russian ruble employs alloys of copper-nickel clad steel, nickel-brass, and brass, the latter being DMG test negative [5]. The Chinese yuan includes aluminum, stainless steel, brass-plated steel, and nickel-plated steel, with only the latter found to release nickel by the DMG test. The Indian rupee alloys of aluminum and stainless steel also commonly test DMG negative. No coins from Brazil, Bolivia, or Costa Rica tested DMG positive [5]. Overall, 40% of coin denominations in circulation do not release nickel [5].

16.4 Methods for the Detection of Metal Release and Coin Composition

16.4.1 Spot Test Analysis: Dimethylglyoxime (DMG) Test and Cobalt Spot Test

The dimethylglyoxime (DMG) test, or nickel spot test, is commonly used to screen for nickel release that exceeds 0.5 μg/cm^2/week [6–8]. In the presence of nickel, the combination of dimethylglyoxime and ammonium result in the formation of nickel glyoximate [9]. Testing is performed by rubbing a cotton-tipped applicator moistened with spot test solution to the surface of a test object for 30–60 s. A positive DMG test is indicated by a pink coloration of the applicator (Fig. 16.1). The DMG test has been validated against EN1811 and found to have a sensitivity of 59% and specificity of 98% [8]. Of note, metals such as aluminum, copper, iron, and zinc are commonly found in coins and may produce colors that mask a weak positive response to nickel, at times resulting in false negatives [5].

The cobalt spot test was developed by Thyssen and colleagues and consists of a 1% aqueous solution of 2-nitroso-1-naphthol-4-sulfonic acid, which can detect cobalt at concentrations of approximately 8 ppm [10]. Testing is performed similarly to the DMG test, and a positive cobalt test is indicated by a yellow-orange coloration of the applicator. The detection threshold is clinically relevant as patients with allergic contact dermatitis to cobalt have been reported to react to concentrations as low as 10 ppm on patch testing [11]. In a global investigation of 850 different coins, none tested positive for cobalt release via the cobalt spot test [5].

16.4.2 X-ray Fluorescence Spectrometry (XRF) and X-ray Photoelectron Spectroscopy (XPS)

X-ray fluorescence, which is widely used for elemental and chemical analysis, can detect common metals and determine the proportion of elements close to the coin surface; however, factors such as metal weight limit the extent of analysis [5]. For example, the Bruker S1 XRF Spectrometer sorter can only detect titanium and heavier metals, so lighter metals such as aluminum cannot be

Fig. 16.1 Coins tested with the dimethylglyoxime test from the six major geographical regions according to the United Nations: a 0.25 US dollar coin (a quarter), a 100 Japanese yen coin, a 1 Argentinian dollar coin, a 2 South African rand coin, a 0.50 Australian dollar coin, and a 0.10 UK pound sterling coin. The *pink color* indicates nickel release. (Reproduced with permission from [5])

detected. Additionally, the spectrometer does not differentiate between plating, clad, and alloy, and metal release is also not assessed [1]. X-ray photoelectron spectroscopy (XPS) can detect outermost coin surface composition better than XRF, but its limitations are similar to XRF [12].

16.5 Metal Release from Coins

Although the majority of the literature focuses on nickel, coins have also been found to be sources of exposure to copper and rarely zinc [13]. Coins have not been found to be a significant source of cobalt release [5].

16.5.1 Copper

Limited data suggest that copper is released from coins and might result in allergic contact dermatitis in select clinical settings. Bronze (50 ore), Nordic gold (10 krona), and copper-nickel (1 krona) coins have been shown to release copper cations at 3 μg/coin, 2.7 μg/coin, and 1.5 μg/coin, respectively, following 2 min of immersion in water [14]. Additionally, a copper migration study immersed coins (95% copper), copper-coated paper clips (0.005%), and copper thread (99.99%) in artificial sweat for 24 h and found a final concentration of 0.01% copper in the solution [15]. As discussed further below (see Wipe Sampling), copper has been shown to be released onto the skin after 3 min of coin handling, as assessed by rubbing the volar aspect of the first three fingers with commercial wipes [13].

A case report described a housewife with a 3-month history of intermittent vesicular dermatitis of the volar fingers and the distal dorsal phalanges [16]. Nickel allergy was suspected, and she had a positive patch test to nickel sulfate 5% pet. As a blue-green discoloration was noted on the inner surface of her coin purse, she was also patch tested with a square of this fabric, as well as copper sulfate 5% aq., both of which gave a 3+ reaction after 72 h. She improved with avoidance of metal contact. Another case report described a bingo hall cashier who developed dermatitis involving the fingertips, upper eyelids, and outer canthi after 12 months of handling 2 euro coins (copper-nickel/nickel-brass) [17]. He described improvement after weekends and vacations. Standard metal patch testing showed a positive reaction only to copper sulfate 5% pet.

16.5.2 Nickel

Several studies have investigated nickel release from coins, as summarized in Table 16.4. In the remainder of the chapter, we will focus primarily upon data regarding nickel release from coins.

16.5.2.1 Experimental Factors Affecting Nickel Release

Nickel release from coins is strongly influenced by the alloy and may be increased by higher temperature, artificial sweat, longer immersion times, and lower pH (Table 16.4) [1, 18–24]. There are likely other factors at play as well: for example, Jellesen et al. showed that the inner nickel-brass portion of the 2 euro released less nickel when subjected to corrosion by artificial sweat in combination with friction, as compared to corrosion only [24]. The authors attributed this somewhat counter-intuitive finding to factors in the design of their in vitro model; nevertheless, this study highlights the need for models that take into account other factors in addition to corrosion when assessing for nickel release from items in short repetitive contact such as coins.

Alloy

It is important to note that nickel release does not directly correlate with a given alloy's nickel concentration but is rather governed by the galvanic properties of metals within the alloy [18]. For example, pure nickel coins have often been found to release lower quantities of nickel relative to copper-nickel coins (Table 16.4).

Water vs. Artificial Sweat

Sweat is well known to possess corrosive effects [19, 20], and greater nickel release has been demonstrated in artificial sweat compared to water. This has been shown in alloys including copper-

Table 16.4 Nickel release from coins under various conditions (Reproduced with permission from [1])

Alloy and plating	Coin	Test conditions for immersion: solvent/temperature/duration	Released amount of Ni (mean)/surface area/time	Reference
Copper-nickel (25% Ni)	1 krona	Distilled water/24 h	15 μg/coin/24 h	[19]
Silver in CuNiZn (5% Ni)	1 krona		49 μg/coin/24 h	
Copper-nickel	1 krona	Artificial sweat/24 h	137 μg/coin/24 h	
Silver in CuNiZn	1 krona		96 μg/coin/24 h	
Copper-nickel	1 krone	Distilled water/20 °C/24 h	20 μg/coin/24 h	[21]
		Artificial sweat/20 °C/24 h	409 μg/coin/24 h	
		Artificial sweat/35 °C/24 h	691 μg/coin/24 h	
Copper-nickel and nickel-brass	2 euro	Artificial sweat/2 min	0.23–0.84 μg/cm²/2 min (four laboratories)	[22]
		Water/2 min	0.03–0.13 μg/cm²/2 min (four laboratories)	
		Artificial sweat/1 week	23–65 μg/cm²/week (four laboratories)	
Copper-nickel	1 krona	Artificial sweat/20 °C/2 min	0.98 μg/coin/2 min	[14]
Cu-plated steel	2 pence		0.19 μg/coin/2 min	
Copper-nickel	10 pence		1.2 μg/coin/2 min	
Copper-nickel	20 pence		1.5 μg/coin/2 min	
Nickel-brass	1 pound		3.4 μg/coin/2 min	
Aluminum-bronze	10 centime		0.14 μg/coin/2 min	
Nickel	1 franc		2.8 μg/coin/2 min	
Bronze	50 ore		0.09 μg/coin/2 min	
Copper-nickel	1 krona	Artificial sweat/30 °C/1 week	38 μg/cm²/week	
Nordic gold	10 krona		0.09 μg/cm²/week	
Cu-plated steel	2 pence		Not detected	
Copper-nickel	10 pence		28 μg/cm²/week	
Copper-nickel	20 pence		14 μg/cm²/week	
Nickel-brass	1 pound		15 μg/cm²/week	
Aluminum-bronze	10 centime		2.2 μg/cm²/week	
Nickel	1 franc		4.3 μg/cm²/week	
Bronze	50 ore		Not detected	
Cu-plated steel	50 cent	EN 1811 (conditions not specified)	Not detected	[20]
Copper-nickel and nickel-brass	1 euro		Approximately 120 μg/cm²/week	
	2 euro		Approximately 160 μg/cm²/week	
Copper-nickel	1 krona	Artificial sweat/20 °C/2 min	0.11 μg/cm²/2 min	[23]
Copper-nickel and nickel-brass	1 euro		0.25 μg/cm²/2 min	
	2 euro		0.22 μg/cm²/2 min	
Copper-nickel	1 krona	Artificial sweat/30 °C/1 h; 24 h; 1 week	4.3, 52, 121 μg/cm²/h, 24 h, week	
Copper-nickel and nickel-brass	1 euro	Artificial sweat/30 °C/1 week	86 μg/cm²/week	
	2 euro		99 μg/cm²/week	

(continued)

Table 16.4 (continued)

Alloy and plating	Coin	Test conditions for immersion: solvent/temperature/duration	Released amount of Ni (mean)/surface area/time	Reference
Copper-nickel and nickel-brass	2 euro	Aqueous solution, initial pH range between 2 and 11/25 °C/1 week	2 euro released more nickel than 2 franc/week at pH between 3 and 10	[13]
Nickel	2 franc			
Copper-nickel and nickel-brass	2 euro	Rubbing coins with commercial skin wipes to assess amount of nickel available on surface	5 μg/coin	
Nickel	2 franc		12 μg/coin	
Nickel-brass	2 euro (inner part)	Corrosion with artificial sweat/1 h	211 μg/cm^2/h	[24]
		Corrosion combined with friction (tribocorrosion)/1 h	37 μg/cm^2/h	

nickel, nickel-brass, silver-copper-nickel-zinc, and pure nickel [14, 19, 21, 22]. For example, the copper-nickel 1 krona released 9 to 20 times more nickel in artificial sweat over 24 h than in distilled water [19], and the 2 euro released 7 times more nickel when washed with artificial sweat compared to water [22]. Therefore, studies conducted in water may underestimate the quantity of nickel released from coins.

Temperature

Greater nickel release occurs at higher temperatures. Menné et al. showed that nickel release from the copper-nickel 1 krona coin was 1.7 times greater at a temperature of 35 °C compared to 20 °C after 24 h of immersion in artificial sweat [21]. The EN 1811 guidelines recommend that immersion studies investigating nickel release be conducted at a temperature of 30 °C [7].

Duration of Immersion

Longer periods of immersion have been associated with greater nickel release from different alloys such as copper-nickel, copper-brass, and pure nickel [14, 22, 23]. Lidén et al. showed that after 2 min of immersion, nickel-containing alloys released on average 2 μg/coin [14]. After 1 week, they released on average 20 μg/cm^2 (range 4–38 μg/cm^2). Of note, non-nickel-containing alloys released 0.15 μg nickel per coin after 2 min of immersion, which was attributed to possible surface cross-contamination from other coins in circulation [14].

The copper-nickel 1 krona and the copper-nickel/nickel-brass 1 and 2 euro have been found to release on average 0.2 μg/cm^2 after 2 min and 102 μg/cm^2 after 1 week [23]. Evaluation of intermediate immersion durations showed that the rate of nickel release slowed over time: for example, the copper-nickel 1 krona released on average 4 μg/cm^2 after the first hour and 52 μg/cm^2 after the first day. As it was observed that coin surfaces following 1 week of immersion were visibly corroded, whereas surfaces after 2 min were not grossly altered, it was hypothesized that the decrease in nickel release rate over time might be due to the highest concentrations of nickel being at the surface of the coin. This would be supported by XPS data [24].

The EN 1811 recommends immersion times of 1 week for studies investigating nickel release [7]. It should be noted that shorter immersion times have been suggested to be more relevant than 1 week of immersion for objects that are not used in prolonged contact but rather in short repetitive contact, such as coins [1]. For example, Julander et al. showed that initial release rates from nickel-plated coins were 10–27 times higher than rates at 1 week, demonstrating that even brief and repeated contact results in significant nickel exposure [12]. Other studies have also

shown significant nickel release within 2 min from coins of copper-nickel, nickel-brass, and pure nickel (1–3 μg/coin or 0.1–0.3 μg/cm^2) [22, 23, 25].

pH

Both the copper-nickel/nickel-brass 2 euro and the pure nickel 2 franc have been shown to release nickel in aqueous solution with a pH ranging from 3 to 10 [13]. Strongly acidic sweat may enhance nickel release, as pure nickel released 100 times more nickel at a pH of 2–3 compared to a neutral pH.

16.5.2.2 Nickel Deposition on the Skin from Coin Handling

Nickel deposition has been demonstrated on the hands with coin handling (Table 16.4), in amounts that have previously been deemed sufficient to elicit hand dermatitis in nickel-allergic patients [1, 26]. Three sampling methods have largely been used to assess nickel deposition on the skin: hand washing, finger immersion, and wipe sampling.

Hand Washing

Initially, nickel deposition from coins was demonstrated by analyzing metal contamination of water used to wash hands after handling coins [19]. Coins were handled for 5 min and hands were then washed with nickel-free soap. Nickel was detected after the handling of both ether-washed and used 1 krona coins, but cobalt was not detected [19].

Finger Immersion

In the finger immersion method, after coin handling, fingers are immersed in ultrapure water that is chemically analyzed for nickel content [27, 28]. With this method, nickel deposition has been shown to occur in direct proportion with the amount of time spent rubbing pre-cleaned coins, ranging from 10 s to 10 min [27]. Additionally, nickel deposition was demonstrated on the fingers of cashiers, ranging from 6.3 to 65 ng/cm^2, although higher nickel levels were found on nickel refinery workers and platers. Of note, Gawkrodger et al. showed that the finger immersion method underestimated nickel deposition by averaging the amount of nickel over the whole finger and therefore not taking into account that most nickel is deposited on the volar fingertips: in fact, they found that localized deposition on the fingertips was tenfold higher than initially calculated via total finger immersion and further refined the technique by introducing a correction factor [28]. Corrected mean nickel levels in cashiers were 0.15 μg/cm^2 after at least an hour of work, in comparison to 0.058 μg/cm^2 in office staff.

Wipe Sampling

Fournier et al. showed that 2 euro (copper-nickel/nickel-brass) and 2 franc (pure nickel) coins released nickel, copper, and zinc when manipulated for 3 min, as assessed by rubbing the volar aspect of the first three fingers with commercial wipes [13]. The coins were also shown to release nickel, copper, and zinc when rubbed directly with commercial skin wipes to assess the amount of metals available on coin surfaces. Notably, low amounts of copper and zinc were detected on wipes from pure nickel coins as well, indicating likely contamination from contact with other coins. When coins were polished prior to manipulation, nickel and copper contamination of fingers was reduced by over tenfold, although the same effect was not seen when coins were washed rather than polished. The authors concluded that the major source of metal transfer during manipulation, such as friction due to everyday usage, was preexisting metallic species present on the surface of coins.

Subsequently, Lidén et al. developed acid wipe sampling, which entailed sampling the fingertips after coin handling with a 1% nitric acid solution on a cellulose wipe, extracting metal ions from the wipes, and chemically analyzing the extraction solution [29]. The method does not utilize commercial wipes, which have an unknown chemical composition that would thus complicate chemical analysis. Acid wipe sampling has shown a greater than 90% recovery of

nickel, chromium, and cobalt deposited on the fingertips and forearms [25, 29].

Acid wipe sampling has been used to demonstrate significant nickel deposition especially on the fingers from both the copper-nickel 1 krona and copper-nickel/nickel-brass 2 euro after even 1 h of handling, with nickel levels ranging from 0.09 to 4.1 μg/cm^2 [23]. Greater deposition was also shown on the fingers of cashiers as compared to secretaries and carpenters after 1 h of work (0.2 μg/cm^2/h vs. 0.018 and 0.077 μg/cm^2/h, respectively) [14]. Generally, nickel deposition was greater on the fingers than the palms, and negligible levels of cobalt and chromium were detected relative to nickel [25], in contrast to similar studies conducted in metal workers [30].

16.5.2.3 Coin Handling and Allergic Contact Dermatitis to Nickel

Patch Test Reactivity to Coins

Patch testing remains the gold standard for establishing contact sensitization to a given allergen, and there have been numerous reports of nickel patch test positivity upon testing directly to nickel-containing coins [31–36]. In 1984, Fisher also reported positive results in two nickel-allergic patients exposed to nickel-containing coins placed under a glove for 24 h, simulating patch testing under occlusion [31]. In addition, reactivity has been demonstrated to 1 euro coins placed for 48 h on the volar forearms, although the thenar and palmar sides of the thumbs resulted in few positives in the same series of 10 nickel-allergic individuals [34].

When investigating European coins in circulation, Nucera et al. reported a greater incidence of positive patch tests to nickel-releasing coins relative to coins that released less nickel [36]: 19 of 25 nickel-allergic patients had positive patch test reactions to 1 and 2 euro coins (copper-nickel and nickel-brass), 13 to the 500 lire coin (aluminum-brass, stainless steel), 4 to the 50 euro coin (Nordic gold), 1 to 1 and 2 euro cent coins (copper-covered iron), and none to the 100 lire coin (stainless steel). In a similar study, Seidenari reported more intensely positive patch test reactions to the 1 and 2 euro compared to the 500 and 200 lire (which contain 2% nickel) and reported only weak erythema in other coins without nickel (20 and 5 euro cent, 100 and 50 lire) [35]. Patients with the strongest reactivity to 1 and 2 euro coins reacted to the lowest nickel concentrations. An older study from Morgan et al. also correlated patch test reactivity to nickel sulfate with exuberantly positive patch test reactions to coins in eight patients [32]. Thus, nickel seems responsible for the majority of patch test reactions to coins.

Case Reports

In 1931, Rothman first reported a case of recalcitrant dermatitis involving the hand, forearm, shoulders, and neck in a German coin counter, who was diagnosed with nickel allergy after being directly tested to coins for 24 h. He cleared a month after the cessation of counting coins [37]. Since then, other reports of patients with hand eczema and primarily occupational exposures to coins have continued to emerge, including over 20 cashiers, [38–48], a bingo hostess [49], a housewife [16], and most recently a taxi driver [50]. In many of these cases, the patients had a known history of nickel allergy [38, 41–43]. The dermatitis presented primarily on the fingers and oftentimes the palms and in general resolved with vacations from coin handling. One case of primary sensitization to nickel was suspected in a female cashier [40]. Another female cashier with positive patch test reactivity to coins had a nickel-containing coin applied to her palms for 20 min, followed by avoidance of hand washing for 4 h, with development of hand erythema at 24 h inspection [38]. Non-occupational exposures have also been reported, including a patient who developed nose and finger dermatitis from rubbing a coin on his nose when it itched, as well as a patient with finger dermatitis where he often stored a coin in the finger of his glove [31].

Dermatitis and Exposure to Coin Handling

Several large-scale epidemiologic studies have shown higher incidences of hand dermatitis in those occupationally exposed to coins on a daily basis [22, 45, 51–54], although these studies are

likely limited by confounding factors that may predispose to hand eczema, such as atopic dermatitis, xerosis, other contact allergies, wet work, and genetic predisposition. Notably, most studies reported a higher incidence of nickel allergy in cashiers relative to the general population [22, 45, 51, 53]. One study reported a much higher incidence in hairdressers relative to cashiers (23.9 vs. 2.9/100,000 people) but overall still attributed an estimated 12% of occupational contact dermatitis to nickel hypersensitivity and possibly to repetitive coin handling [53].

Prospective studies have demonstrated hand eczema exacerbated by nickel exposure [55], such as from prolonged coin exposure with nickel-containing alloys [56, 57]. In 1997, the Royal Swedish Mint conducted a blinded prospective provocation study in Denmark, Italy, The Netherlands, Spain, Switzerland, and Sweden, wherein 40 nickel-sensitized patients with ongoing hand eczema stacked 1 or 10 krona coins for 4 h [57]. Forty-eight hours after coin handling, 14 of 21 patients in the 1 krona group and 9 of 19 patients in the 10 krona group were noted to have worsening of hand eczema. In addition, 3 nickel-allergic cashiers with suspected occupational exacerbation of hand eczema counted cupronickel coins for 15 min per day without washing their hands until the next morning, and 2 developed dermatitis on the fingers and palms after 2–3 days while the third did not develop dermatitis after 5 days [56].

Others have found no increased incidence of hand eczema with exposure to nickel-containing coins. In 1975, Christensen et al. reported 12 nickel-allergic pompholyx patients who experienced no worsening of eczema after stirring their hands in a jar of mostly Swedish (copper-nickel) silver coins, along with other nickel-releasing objects, for 6 min [58]. It is important to note, however, that 6 min of exposure time may not be sufficient to elicit dermatitis, especially when compared with the prolonged exposure times typically encountered in the occupational setting. Zhai et al. in a blinded controlled crossover study also found no worsening of hand eczema after 18 nickel-sensitized or non-sensitized subjects handled Canadian 5 cent (copper-nickel) or 1 cent (copper-plated zinc) circulating coins for 5 min intervals, 8 h a day for 12 days [59]. Outcome measures included evaluation for erythema, transepidermal water loss, blood flow volume, and other signs of dermatitis in the hands. The authors concluded that, although they did not observe an increase in dermatitis, perhaps the contact simulated in the study was too brief and did not account for various occupational factors that may elicit hand dermatitis, such as humidity, sweat, and friction.

16.6 Regulatory Efforts

Regional nickel allergy prevalence plays an important role in determining rates of coin-related allergic contact dermatitis and is in large part determined by the amount of nickel found in day-to-day exposures such as jewelry and clothing, which is subject to legislation. Of note, the 1994 European Union (EU) Nickel Directive limited nickel release from objects meant for direct and prolonged exposure [1, 60]; in 2009, this was subsumed into the REACH regulation and has continued to be successful in decreasing rates of nickel allergy in Europe [61]. Unfortunately, coins have not been addressed as these were not felt to be subject to direct and prolonged exposure in the general public. In 1997, the European Commission concluded that the limited data available suggested that a few cases of dermatitis may have been caused by nickel release from the coins in circulation at that time and that workers handling coins appeared to have a low risk of occupational dermatitis [62]. They also went on to state that further studies were necessary "to obtain statistically significant evidence concerning the eventual role of nickel release from coins in relation to aggravation of hand eczema." Unfortunately, further studies have not been undertaken by the European Commission as of the time of this publication [1, 60].

In 2011, Her Majesty's Treasury of the United Kingdom concluded that conversion of 5 pence and 10 pence copper-nickel coins to nickel-plated

steel coins for cost saving purposes would have no impact on public health. This was based on a statement made by the Royal Mint that no risk assessment had been undertaken on the coins as they were not governed by legislation and as contact was not prolonged [1]. Julander et al., however, later showed that 1 h of handling the new nickel-plated coins resulted in the deposition of four times as much nickel on the skin (7.5 μg/cm^2) than the previous copper-nickel coins, as a result of higher nickel content in the oxidized surface of the nickel-plated coins [12].

Currently, Sweden has been the only country to restrict nickel from coins due to allergy risk. In 2011, the Swedish Riksbank declared that all new coins would be made of copper-plated steel and Nordic gold [1], to be implemented from 2016 and on.

16.7 Conclusion

In conclusion, coins appear to be a relevant source of exposure to copper and especially nickel and may result in exacerbation or elicitation of dermatitis in select clinical settings. Allergic contact dermatitis to coins is dependent on many variables, including alloy; local factors affecting nickel release (e.g., humidity, temperature, pH); duration, type, and frequency of exposure; skin barrier factors affecting individual susceptibility (e.g., xerosis, preexisting hand dermatitis); as well as baseline nickel allergy prevalence for the region. Patients who handle coins occupationally and consumers with nickel allergy appear to be at particular risk. Altogether, coins should be considered a potential source of exposure to metal allergens. Further studies are required to better evaluate the extent of sensitization and/or dermatitis caused by coinage.

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Metals in the Diet

17

Matthew J. Zirwas

17.1 Nickel

Approximately 20% of patch-tested patients in the United States are allergic to nickel [1]. Many double-blind, placebo-controlled studies have shown that oral challenge with nickel leads to clinical symptoms more frequently in those with positive patch test reactions to nickel than in those with negative patch test reactions to nickel. This chapter will briefly review the evidence that oral nickel causes clinical symptoms but will focus on describing what is known about the pathophysiology of these reactions and their treatment.

In this chapter, the term systemic contact dermatitis to nickel (SCDN) will refer to skin-limited symptoms and findings induced by nickel consumption, while the term systemic nickel allergy syndrome (SNAS) will refer to the combination of skin symptoms and findings with associated systemic symptoms, primarily of the gastrointestinal (GI) tract.

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17.2 Evidence that Nickel Consumption Leads to Clinical Symptoms

There is a substantial body of evidence demonstrating that dietary nickel causes clinical symptoms, so substantial in fact, that there can no longer be a question of whether this phenomenon exists. Briefly, though, there are two obvious types of evidence that dietary nickel consumption leads to clinical symptoms: (1) development of clinical symptoms with oral nickel challenge, especially when the challenge is double-blind, placebo controlled, and (2) resolution of clinical symptoms with dietary nickel restriction.

17.2.1 Development of Clinical Symptoms with Oral Nickel Challenge

Numerous studies have demonstrated that oral challenge with nickel, typically as nickel sulfate, leads to flares of clinical symptoms in patients who have positive patch tests to nickel, with the percentage of patients having cutaneous symptoms with challenge increasing with the dose [2–12]. A dose-response relationship has also been shown for systemic symptoms resulting from oral challenges [13]. A meta-analysis of nickel challenge studies found a clear dose-response relationship, with it being estimated that roughly 10% of nickel-allergic patients will

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have a reaction to an oral challenge with 1 mg of elemental nickel [5].

The likelihood of reacting to oral nickel challenge does not appear to correlate with how sensitive the patient is to nickel patch testing, as when serial dilutions of nickel were used for patch testing and serial doses of oral nickel were used for oral challenge, there was no correlation between the minimum concentration that caused a patch test reaction and the likelihood of reacting to oral challenge or the oral dose needed to cause a reaction [14]. Another study did find a correlation between the intensity of patch test reactions and the likelihood of responding to an oral challenge [6].

In those with a positive oral challenge, the likelihood of improving on a low-nickel diet is higher in those with 1+ or 2+ patch test reaction than in those with 3+ reactions [15].

Most studies use challenges with nickel sulfate and can be criticized because the dose of nickel used is higher than could be consumed in a single meal. There are fewer studies that look at challenge with a diet naturally high in nickel. In one such study, 12 nickel-allergic patients were challenged in a blinded manner with a high-nickel diet for 4 days (containing almost 500 ug/d of nickel). Urinary nickel excretion quadrupled while on the diet. At day 4, 50% flared based on both patient and investigator assessment, and at day 11 (7 days after the dietary nickel challenge had ended), 100% had flared based on both patient and investigator assessment [16].

17.2.2 Improvement of Symptoms with Reduction in Dietary Nickel Intake

Numerous studies have demonstrated that a substantial percentage, usually in the range of 40%, of patients with a positive patch test to nickel and widespread dermatitis or hand dermatitis improve when placed on a low-nickel diet [11, 15, 17–19]. If the group put on a low-nickel diet is limited to those who also have a positive oral challenge to nickel, the likelihood of improving on the diet rises to the 60–80% range [12, 20]. Studies showing improvement on oral disulfiram do not truly offer evidence that dietary nickel is the causative factor, as while there is evidence that disulfiram chelates nickel out of the body, it has not been proven that there isn't some other effect of disulfiram that leads to the improvement.

17.3 Pathophysiology of Systemic Contact Dermatitis to Nickel

There are two primary aspects of understanding SCDN and SNAS: (1) understanding the normal physiology of nickel in the body – its absorption in the GI tract, transport in the body, and excretion – and (2) understanding the immunologic reaction to ingested nickel in nickel-sensitive individuals who react to dietary nickel, both the specific effects on the immune system and the reason(s) why only some nickel-sensitive patients react.

17.3.1 Nickel Physiology

Nickel is a component of numerous foods, and it is estimated that the human body contains 10 mg of nickel [21, 22]. Estimates of daily intake of nickel vary from country to country, with estimates of up to 4 mg per day in some Swedish diets (although with an estimated average consumption of 0.75 mg) [23]. In the United States (USA), a reasonable average daily dietary nickel intake is in the range of 0.5 mg.

Some foods are generally high in nickel, but the nickel content of any given food can vary widely based on the nickel content of the soil where the food was produced [22]. In general, whole grains, legumes, and cocoa beans are very high in nickel. Urinary nickel levels increase directly in proportion with ingestion of nickel-rich foods [24]. Between 10 and 40% of the nickel consumed is absorbed, and nickel absorption may be greater in patients over age 30 [23–25]. Taking dietary supplements and drinking water that has been stagnant in nickel-containing pipes increases systemic nickel exposure as well [24].

The foods that are co-ingested with nickel also affect absorption, although comprehensive studies of which foods and drinks affect nickel absorption and how they affect it are lacking – for example, milk, orange juice, tea, and coffee reduced nickel absorption compared to ingestion with water, while ingestion with Coca-Cola did not [23]. Ingestion with phytic acid did not affect nickel absorption, ingestion with ascorbic acid (vitamin C) reduced nickel absorption, and ingestion with disodium ethylenediaminetetraacetic acid (EDTA), a common food preservative, led to a dramatic drop in nickel absorption and even a drop in serum nickel levels [23].

When nickel is given orally on an empty stomach, the nickel blood level peaks between 1.5 and 4 h and remains elevated for up to 96 hours [23, 25]. There is a 20% variation from individual to individual in the rise in serum nickel in response to a given dose of oral nickel [23]. With increased nickel ingestion over long periods of time, the proportion of nickel that is absorbed declines [26].

Absorbed nickel is excreted primarily in the urine, with between 50% and 80% of absorbed nickel being excreted in the urine [25]. Urinary nickel rises in proportion to the serum nickel [27]. Renal excretion of nickel increases with increases in nickel ingestion [26].

Nickel is also excreted in the sweat, with nickel concentration in sweat being substantially higher in women than in men, but nickel concentration in sweat does not correlate with nickel concentration in blood or urine [27, 28].

While there is conflicting data, nickel sensitization does not seem to affect nickel absorption in the GI tract nor renal excretion, as when allergic and nonallergic women were challenged with oral nickel, there were no differences between the groups in the resultant increases in serum and urinary nickel [29, 30]. In addition, urinary nickel levels were the same in sensitized and non-sensitized groups [24]. In one study, individuals with positive nickel patch tests had higher serum nickel levels at baseline [31].

Atopic dermatitis does appear to affect nickel metabolism, as serum nickel levels increased more in atopic patients in response to an oral nickel challenge than in non-atopics [32]. Specifically, patients with intrinsic atopic dermatitis (IAD), defined as meeting the Hanifin and Rajka criteria but having a normal IgE level and not being sensitized to dust mite, had a serum nickel concentration that was double that in extrinsic atopic dermatitis (EAD) patients and seven times that of healthy controls [33]. In another study, IAD patients were nearly three times as likely to be nickel sensitized as EAD patients, and the IAD patients had over three times higher nickel concentrations in their sweat compared to EAD patients [34]. These data may be interpreted in two ways: (1) that some proportion of patients diagnosed with IAD really have SCDN or (2) that patients with IAD truly differ from those with EAD in terms of nickel metabolism.

17.3.2 Immunologic Response to Ingested Nickel

When the cutaneous reactions to ingested nickel are biopsied, the histology is similar to regular allergic contact dermatitis (ACD) to nickel, with infiltrates consisting primarily of CD4+ T-cells and smaller numbers of CD8+ T-cells [35, 36]. In patients who react to an oral nickel challenge, there is a drop in blood monocytes at approximately 4 h after the challenge and then a marked decrease in blood B-cell and T-cell counts at 24 h [30, 37]. More specifically, patients who have a reaction to oral nickel show decreases in CD3 + CLA+ (but not CD3 + CLA-), CD4 + CD45RO+, CD4 + CD45RO-, CD8 + CLA+ (but not CD3 + CLA-), CD19+, and CD5-CD19+ lymphocytes [7, 30, 37].

When cytokine levels are followed, there is a statistically significant increase in IL-5 in the nickel-allergic patients who react to oral nickel compared to those who do not react to oral nickel [7]. IL-6 and IL-10 also increased in these patients but did not reach statistical significance [7]. IL-2, IL-4, TNF-alpha, and IFN-gamma did not increase in the nickel reactors [7].

When duodenal biopsies were performed 2 days after nickel challenge, those who reacted to oral nickel challenge showed dramatic inflammation compared to non-nickel-sensitive patients

and nickel-sensitive patients who didn't react to the oral challenge. The infiltrating cells were mainly CD45RO+ [37].

Finally, when nickel patch test positive patients with urticarial, respiratory, oral, and/or skin symptoms that were thought to be related to dietary nickel were studied with prick testing, 70% of patients had positive prick tests to 10 mg/ml nickel suspension compared to 30% of controls, with the urticarial patients being the most likely to have a positive prick test [17]. When lymphocyte transformation testing was performed with nickel as the stimulating agent, patient lymphocytes showed elevated production of IL-4, IL-5, IL-10, and IFN-gamma compared to controls [17].

In summary, it appears that in patients who react to an oral challenge, circulating lymphocytes are activated in response to nickel in the blood, migrating into the gut mucosa and skin and producing IL-4, IL-5, and IL-10.

17.4 Treatment of SCDN and SNAS

There are four potential treatment approaches: (1) reduce the amount of nickel ingested, (2) reduce the amount of ingested nickel that is absorbed in the GI tract, (3) remove nickel from the body, and (4) desensitize the immune system. Each approach has been shown to have efficacy, although there are not well done head-to-head trials.

17.4.1 Reduction of the Amount of Nickel Ingested

As previously noted, around 40% of patients with a positive patch test to nickel and suspected reactions to dietary nickel will improve when placed on a low-nickel diet [11, 15, 17–19]. Limiting it to those who respond to an oral nickel challenge increases the likelihood of improving to the 60–80% range [12, 20]. For patients in the United States, the most recently published low-nickel diet based on a point system is recommended (Table 17.1) [22]. Because the mineral content of foods varies based on the geographic area where the food was produced, it is uncertain how accurate this diet would be for those living in other parts of the world.

Two fundamental questions are (1) why don't all nickel-allergic patients react to a nickel challenge and (2) why don't all patients who react to an oral challenge improve on a low-nickel diet. Evidence does not exist to definitively answer these two questions, but there are hypotheses that can be drawn based on interesting findings. First, in one of the oral challenge studies, the patients who reacted to the oral challenge had a greater rise in urinary nickel than those who didn't [13]. The most likely explanation was that those who reacted either absorbed more of the nickel from the challenge or ingested additional nickel via their regular diet in the days preceding and following the challenge. In another study, urinary nickel levels dropped more consistently and to a greater degree in those who improved on the diet compared to those who did not, although this did not reach statistical significance (likely due to small sample size) [9]. In a patient who was carefully followed, serum and urine nickel levels dropped by half while on the low-nickel diet, and timing of the improvement in symptoms correlated with the timing of the drop in nickel levels [38]. Overall, the literature suggests that (1) variation in the amount of nickel actually absorbed into the blood, either because of differences in what proportion of nickel is absorbed or because of differences in nickel ingestion related to diet, is the primary determinant of who responds to a nickel challenge; and (2) inability to adequately lower systemic nickel exposure, either due to poor compliance with the diet, living in a region that has high nickel content in food and water due to soil concentration, or having an intestinal system that absorbs a higher proportion of ingested nickel than normal, or some other factor, is the primary reason for failure of patients to improve on a low-nickel diet [12].

Table 17.1 Instructions for low-nickel diet (Reproduced with permission from [22])

Instructions for following low-nickel diet:

1. It may take up to 2 months to see the benefits from following this diet.
2. Adults should consume no more than 15 points per day.
3. Children under age 12 should consume no more than 10 points per day.
4. Very rare individuals are even more sensitive than this and may need stay under 5 points per day.
5. In general, even if not listed specifically, avoid anything with beans, chocolate, peanuts, soy, oatmeal, or granola.
6. Only distilled water should be consumed, either by drinking or in cooking. It is fine to bathe or shower in regular tap water.
7. Avoid cooking acidic foods in stainless steel cookware. Acidic foods include tomatoes, vinegar, and citrus. Types of cookware that are safe: nonstick coated of any type, aluminum, copper, or cast iron.

Apple juice	1
Apple pie	2
Apples	1
Applesauce	1
Apricots	3
Arctic char	0
Asparagus	3
Avocado	2
Bacon	1
Bagel, plain	1
Banana	1
Beans	1
Beans, brown dried white	7
Beans, white	6
Beef	0
Beef stroganoff with noodles	3
Beef with vegetables in sauce	4
Beer	0
Beets	1
Biscuits	2
Black currants	1
Blueberries	0
Bologna	1
Bread, wheat or rye	2
Bread, white	1
Bread, whole wheat	1
Broccoli	1
Brownie	6
Brussels sprouts	1
Buckwheat	6
Burrito with beef, beans, cheese	8
Butter or margarine	0
Cabbage	1
Cake, chocolate with icing	Avoid
Cake, yellow with icing	2
Candy bar, chocolate, nougat, nuts	2
Candy, hard	0
Cantaloupe	2
Carrot	1
Catfish	2
Cauliflower	1
Celery	1
Cereal, corn flakes	1
Cereal, cream of wheat	1
Cereal, crisped rice	2
Cereal, fruit flavored	3
Cereal, granola with raisins	6
Cereal, oat ring	Avoid
Cereal, raisin bran cereal	1
Cereal, shredded wheat	1
Cheese, American, processed	1
Cheese, cheddar	0
Cheese, Swiss	0
Chick peas	6
Chicken	1
Chicken breast, fried with skin	1
Chicken breast, skin removed	0
Chicken filet sandwich-broiled	2
Chicken leg, fried with skin	1
Chicken nuggets, fast-food	3
Chicken potpie, frozen	4
Chicken with vegetables in sauce	3
Chicken, roasted skinless	1
Chili with beans, canned	Avoid
Chocolate	6
Chocolate chip cookies	2
Chocolate syrup	6
Chocolate, bitter	3
Chocolate, milk	1
Chuck roast, beef	1
Clam chowder	4
Cocoa powder	9
Cod	0
Coffee	1
Coffee creamer, nondairy	0
Coffee, decaffeinated	1
Coleslaw	1
Collards	1
Cookies (Oreo type)	2
Cookies, sugar	1
Corn	2
Corn/hominy grits	1
Cornbread	1

(continued)

Table 17.1 (continued)

Cottage cheese	0
Crackers (non-whole wheat)	1
Cranberry juice cocktail	1
Cream cheese	0
Cucumber	1
Currants	0
Doughnut	3
Eggplant	0
Eggs	0
Endive	1
English muffin – egg, cheese, ham	2
English muffin, plain	1
Fish	3
Fish sandwich, fast food	2
Fish sticks or patty	2
Flaxseed	1
Flour, white	0
Flour, whole wheat	1
French fries	4
Fruit cocktail, canned	4
Fruit drink	0
Fruit juice	1
Granola bar with raisins	5
Grape juice	1
Grapefruit	1
Grapefruit juice	2
Grapes	1
Gravy, canned or bottled	1
Green beans	2
Half and half cream	0
Ham, cured, baked	1
Hamburger	2
Honey	0
Hot dog	1
Ice cream, vanilla	0
Jello	0
Jelly	0
Kale	1
Lamb	1
Lamb chop	1
Lasagna with meat	7
Leeks	1
Lemonade	1
Lentils, green	Avoid
Lettuce	2
Lima beans	Avoid
Liver	1
Liver (beef/calf)	1
Lunch meat (chicken, turkey, or ham)	0
Lunch meat, salami	1
Macaroni and cheese	1
Macaroni salad	1
Maple syrup	0
Mayonnaise	0
Meal replacement shake	3
Meatloaf	1
Milk shake, chocolate	8
Milk, chocolate	4
Milk	0
Mixed vegetables	2
Muffin, fruit or plain	1
Mushrooms	1
Noodles, egg	1
Oatmeal	10
Oats, raw	4
Okra	1
Olive oil	0
Olives	1
Onion	1
Orange	1
Orange juice	1
Pancakes	2
Peach	3
Peanut butter	3
Peanuts	5
Pear	2
Peas, frozen	4
Peas, green	1
Peas, split yellow	4
Pepper, green	2
Perch	0
Pickles, dill	1
Pineapple	3
Pineapple juice	6
Pinto beans	Avoid
Pizza, cheese and pepperoni	3
Plums	1
Popcorn	2
Poppy seeds	0
Popsicle	0
Poptart/toaster pastry	2
Pork	1
Pork and beans	Avoid
Pork chop	1
Pork roast	1
Potato chips	1
Potato salad	2
Potato, baked or boiled	2
Potatoes	1

Table 17.1 (continued)

Pretzels	1
Prune juice	7
Pudding, not chocolate	2
Pumpkin pie	3
Raisins	1
Raspberries	1
Refried beans	Avoid
Rhubarb	1
Rice	1
Rice, fried and meatless	3
Rice, white	1
Salad dressing	0
Sausage	1
Sherbet	1
Shrimp	1
Soda/pop/cola	0
Soup, bean, bacon, pork – canned	10
Soup, chicken noodle, canned	2
Soup, oriental noodles – ramen	1
Soup, tomato, canned	4
Soup, vegetable beef, canned	3
Sour cream	0
Soybeans	Avoid
Spaghetti	1
Spaghetti with meat sauce	1
Spinach	2
Squash, summer	1
Squash, winter	2
Steak	0
Stew – beef and vegetable	3
Strawberries	2
Sugar	0
Sugar, brown	0
Sunflower seeds, shelled	Avoid
Sweet and sour sauce	1
Sweet potatoes	2
Sweet roll/Danish pastry	2
Taco/tostada with beef and cheese	3
Tea, decaffeinated	2
Tea, from tea bag	2
Tomato	1
Tomato catsup	1
Tomato juice	4
Tomato salsa, bottled	1
Tomato sauce, bottled	3
Tortilla chips, corn	1
Tortilla, flour	2
Trout	0
Tuna noodle casserole	3
Tuna, canned	0
Turkey breast	1
Turnip	1
Vegetable oil	0
Vegetables, mixed	3
Walnuts	2
Watermelon	3
Wheat bran	0
Wheat germ	1
Whitefish	0
Wine, red/white	1
Yellow mustard	1
Yogurt	2

17.4.2 Reduction of the Amount of Ingested Nickel that Is Absorbed

This has not been attempted as a sole therapeutic approach. There are two approaches, though, that have good data to support their efficacy in reducing nickel absorption. The first is the co-administration of vitamin C (ascorbic acid) with meals. Co-administration of 1 g of ascorbic acid with a dose of nickel sulfate hexahydrate substantially reduced the rise in plasma nickel concentration compared to when the nickel was given by itself [23]. Vitamin C is cheap, widely available, and safe, so taking a chewable vitamin C tablet with every meal is a simple recommendation for clinicians to make and for patients to implement.

Disodium cromoglycate (DSCG) also showed significant efficacy in reducing nickel absorption in a study of 24 patients who were nickel allergic and reacted to a challenge with 10 mg NiSO4 (2.09 mg of elemental nickel) [18]. Patients were randomized to either a low-nickel diet group or a regular diet supplemented with DSCG. Both groups improved clinically and had reductions in urinary nickel, but the DSCG group improved significantly more and had a greater reduction in urinary nickel. On intestinal permeability testing, the DSCG group showed a reduction in osmosis through aqueous pores of enterocytes, with this being the

presumed cause of the reduction in urinary nickel and clinical improvement.

More interesting, and possibly more effective than either of the above, is the ingestion of calcium disodium EDTA with meals. When 40 mg of iron sodium or disodium EDTA were ingested with a dose of 5 mg of elemental nickel (22.4 mg of nickel sulfate), both not only completely blocked the expected rise in serum nickel but actually led to subsequent decreases in serum nickel, suggesting that they bound nickel so tightly that they prevented its absorption and also actually drew nickel from the blood into the intestines where it could be excreted [23]. Calcium disodium EDTA is available at a very low cost, making this a reasonable treatment alternative. However, it is uncertain if it is possible for deficiencies to develop due to other minerals it binds, such as iron or magnesium, so care should be taken if this treatment is recommended, and monitoring of iron, magnesium, and other minerals should be considered.

17.4.3 Removal of Nickel from the Body

There have been several reports of the effectiveness of the oral chelating agent disulfiram, both in conjunction with a low-nickel diet and as a standalone treatment. The combination is more effective and has fewer side effects, although disulfiram used alone is also effective in the significant majority of patients [10, 39–41]. Unlike calcium disodium EDTA, which is very poorly absorbed from the GI tract (approximately 5% absorbed) and is thought to have its effect by binding nickel in the GI tract and preventing absorption, disulfiram is absorbed into the blood and is thought to bind circulating nickel and remove it from the body.

In one of the earlier reports in the literature, it was demonstrated that in alcoholics being treated chronically with disulfiram to prevent alcohol consumption, their serum, blood, and urinary nickel levels all increased. The median increases compared to pretreatment levels were 17 times in serum, 15 times in whole blood, and 39 times in urine [42]. Similar increases were seen in other studies with disulfiram, with the nickel levels remaining elevated in serum and urine as long as the patient stayed on disulfiram [39, 40, 42]. This supports the concept that the disulfiram is binding nickel in the blood and the disulfiram/nickel complex is then excreted in the urine.

It is important to understand that the assays are measuring the total amount of nickel in the serum and urine, not the amount of free nickel. So, while the increase in serum levels could be concerning, this is unlikely because the nickel in the serum is not immunologically active due to binding to diethyldithiocarbamate (active metabolite of disulfiram) [40]. That being said, a substantial proportion of patients will flare, with symptoms ranging from exacerbation of existing dermatitis to significant systemic symptoms and even leukocytoclastic vasculitis, when starting disulfiram, presumably due to a transient increase in the serum concentration of immunologically active free nickel [39, 40]. Whether disulfiram is started at the full dose or started at a lower dose and titrated upward, the majority of patients will still have a flare, with up to 80% of patients being affected [40, 41]. Initiating a low-nickel diet for several weeks prior to initiation of the disulfiram may reduce the likelihood of a flare reaction and reduce the severity of the flare if it does occur [10].

17.4.4 Desensitization to Nickel

Desensitization to oral nickel using progressively increasing doses of nickel has been shown to be effective in a number of studies, being effective in up to 85% of patients [43]. There are two proposed mechanisms, each with experimental support: (1) immunologic desensitization and (2) intestinal alterations that result in reduced nickel absorption.

One study used a stepwise increase in oral nickel dosage: 0.627 mg elemental nickel (3 mg NiSO4) from day 1 to 20, 1.254 mg elemental nickel (6 mg NiSO4) from 21 to 40, and 2.090 mg

elemental nickel (10 mg NiSO4) from day 41 onward (between 49 and 152 days). Nickel-sensitive patients had a higher serum nickel at baseline than nonsensitive individuals, suggesting they absorbed nickel more efficiently. However, nickel serum levels did not increase over the duration of the study and no patients flared, suggesting that as the amount of nickel ingested increased, the proportion that was absorbed decreased [31].

In another similar study, 22 patients with positive challenges to 2.090 elemental nickel (10 mg NiSO4) were treated with 0.627 mg elemental nickel (3 mg NiSO4)/day × 1 month, 1.254 mg elemental nickel (6 mg NiSO4)/day x 1 month, and 2.090 mg elemental nickel (10 mg NiSO4)/day × 1 month. Three had to stop due to flares in the first month (days 4, 8, and 15) but no others flared, even when taking the same dose daily for a month that had previously caused a flare when taken once during the initial oral challenge. Very importantly, there was no effect on patch test reactions or reactions to earrings after completing the 3 months, suggesting strongly that the mechanism of tolerance is not immunologic hyposensitization but instead reduced absorption [2].

Another randomized study showed the importance of dose and frequency of administration in oral hyposensitization and suggested an immunologic mechanism. Patients were treated with either 0.5 mg per day or 5.0 mg per week of nickel for 6 weeks. A single patient in the small daily dose group flared, and there were no changes in patch test reactivity to nickel after 6 weeks. In the high weekly dose, over half had flares and there was a significant reduction in patch test reactivity to nickel after the 6 week treatment course [44].

Very small doses of nickel, 0.5 ng per day, combined with a low-nickel diet, were shown potentially useful in a study completed by 30 out of 50 initial participants. Fewer than 20% had flares, and those who completed the regimen showed a decrease in reactivity to oral challenge, but less than half showed any change in patch test reactivity [45].

In another very low dose protocol, SNAS patients were randomized to either a low-nickel diet only (12 patients) or to a low-nickel diet combined with desensitization using NiOH starting at 0.3 ng per week and titrating up to 1.5 ug per week, which was then continued for 12 months. Patients in the desensitization group had greater clinical improvement and increased tolerance to nickel-rich food after completing the protocol, as well as reduced in vitro peripheral blood mononuclear cell release of IL-13, IL-5, and IFN-gamma in response to nickel stimulation [46]. In a different trial looking at the minimum doses necessary, patients were randomized to 1.5 ug per week, 0.3 ug per week, and 0.03 ug per week for 1 year. The 1.5 ug per week group had improvements in GI symptoms and reduced sensitivity to oral challenge while the other groups did not show similar changes [19].

A higher dose protocol showed more impressive results from desensitization. Twenty-six patients who completed a 3-month protocol taking 50 ug per day showed a significant decrease in patch test reactivity to nickel, improved clinical symptoms, and reduced in vitro T lymphocyte reactivity to nickel. However, this was an open label study, so placebo effects cannot be excluded as the cause of the changes [47].

In the highest quality study reported to date, 141 patients with a positive nickel patch test, symptoms consistent with SNAS, improvement on a low-nickel diet, and a positive response to an oral nickel challenge were randomized to treatment with different doses of nickel in a double-blind, placebo-controlled manner. Dose levels were 1.5 ug per week, 0.3 ug per week, or 30 ng per week (in all cases the total weekly dose was divided into three weekly doses). A low-nickel diet was implemented 1 month prior to beginning oral nickel supplementation, and high-nickel foods were intentionally reintroduced in a gradual manner after 3 months of nickel supplementation. Those in the highest dose group showed improvements in clinical symptoms overall and reductions in patch test reactivity and responsiveness to oral challenge, but the changes did not become apparent until between 7 and 12 months of oral treatment [19].

17.5 Summary: Nickel Allergy and Dietary Nickel

A substantial number of patients with nickel allergy will manifest cutaneous and systemic symptoms related to dietary nickel ingestion in a dose-dependent fashion. It is unclear what the distinguishing factor is between patients who do and do not react to dietary nickel – it may be an immunologic difference or a difference in GI absorption of nickel. In patients who react to oral nickel challenges, there is an increase in IL-4, IL-5, and IL-10 released from T lymphocytes. This happens in the gut mucosa for certain but may be happening in multiple other tissue sites as well.

In the ideal setting, the combination of (1) a diffuse, pruritic dermatitis and (2) a positive nickel patch test would trigger additional testing to confirm the diagnosis of SCDN or SNAS, but such testing is not generally feasible at present. Thus, when the diagnosis is suspected based on criteria (1) and (2) above, a therapeutic trial is appropriate.

Therapeutic options include a low-nickel diet alone or in conjunction with one or more adjunctive therapies, including oral disulfiram, oral disodium cromoglycate, oral calcium disodium EDTA, or oral nickel desensitization. There are no comparative trials to help in determining which therapy is most effective or has the best cost-effectiveness ratio. Unfortunately, disodium cromoglycate is generally not available in appropriate oral doses in the United States to allow its use to be considered, nor are the materials for oral nickel desensitization, so these approaches will not be discussed further.

The author's current approach is to initiate therapy with a low-nickel diet and a 1-month course of calcium disodium EDTA at 600 mg taken three times daily with meals, supplemented with a non-nickel-containing, iron-rich multivitamin taken immediately before bed. Calcium disodium EDTA is available via multiple online sources at a low cost (less than $20 for enough to complete 1 month of therapy). No laboratory monitoring is necessary, and there is essentially no risk of side effects or of a flare of dermatitis. If there is clear clinical benefit, the low-nickel diet is continued and calcium disodium EDTA is repeated if and when symptoms relapse.

Disulfiram therapy is reserved for patients who only respond partially to combined low-nickel diet and calcium disodium EDTA and who relapse quickly when chelation therapy is discontinued. It is typically used at 250 mg/day for 8 weeks while the low-nickel diet is continued. Liver function tests are drawn prior to initiation and are repeated at the 1-month mark. Patients are warned that a flare of cutaneous and/or systemic symptoms is likely and that absolute avoidance of alcohol consumption is necessary. Chelation therapy is continued for 1 month out of every three in an attempt to avoid reaccumulation of nickel and thus to avoid the need for repeated courses of disulfiram.

17.6 Chromium

Chromium is present in most dietary items, and the amount varies substantially based on the soil content where the food is produced [48]. There is substantially less hard data on chromium content of foods compared to nickel, and there is substantially less experimental evidence linking dietary ingestion of chromium to dermatitis, but clinical experience strongly suggests that at least some patients who are patch test positive to chromium will experience clinical exacerbation of dermatitis, vesicular hand dermatitis in particular, with a high-chromium diet and improvement with avoidance of dietary chromium [49–52].

The published information on the chromium content of foods is less comprehensive than for nickel. However, the two sources that seem to be most reliable in recent publication include an analysis by Thor et al. that reviewed the published data on chromium content in food and a study by Anderson et al. that directly measured the chromium content of various foods [48, 53].

17.7 Cobalt

Similar to the situation with chromium, there is much less data for cobalt than for nickel regarding the frequency, mechanism, or management of systemic contact dermatitis from its ingestion in

food. Once again, clinical experience and published studies with oral challenges strongly suggest that at least some individuals who are patch test positive to cobalt will have clinical exacerbation of their dermatitis, especially vesicular hand dermatitis, with a high-cobalt diet and improvement with dietary cobalt restriction [51, 54, 55].

Fortunately, unlike chromium and like nickel, there is a recent, practical, useful article by Stuckert and Nedorost with specific instructions for following a low-cobalt diet (Table 17.2) [56]. The instructions presented in this article are quite useful and user-friendly for patients in whom a low-cobalt diet is recommended.

Table 17.2 Instructions for low-cobalt diet (Reproduced with permission from Stuckert et al. [56])

Instructions for low-cobalt diet[a]			
Points	Food	Serving size–American	Serving size–metric
Avoid	Brazil nuts	1 oz	28 g
	cow liver	4 oz	113 g
	Homeopathic/Herbal Remedies		
7	Flaxseeds	2 tablespoons	13 g or 30 ml
	Garbanzo beans/chick peas	Half of a cup	93 g or 112 ml
	Lamb liver	4 oz	113 g
5	Buckwheat	2 tablespoons	15 g or 30 ml
	Chilli with meat and beans	1 cup	240 g or 224 ml
	Chocolate cake	3 × 3 × 2 inch	95 g or 7.5 × 7.5 × 5 cm
	Chocolate milk	1 cup	240 g or 224 ml
	Chocolate milk shake	1 cup	240 g or 224 ml
	Chocolate powder drink mix	1 packet or 1.3 oz	36 g
	Clam chowder soup	1 cup	240 g or 224 ml
	Lamb kidney	4 oz	113 g
	Millet seeds	2 tablespoons	13 g or 30 ml
	Mixed nuts without peanuts	1 oz	28 g
	Pinto beans	Half of a cup	93 g or 112 ml
	Soy milk	1 cup	240 g or 224 ml
	Sunflower kernels	1 oz	28 g
3	Baked beans	Half of a cup	93 g or 112 ml
	Bean soup	1 cup	240 g or 224 ml
	Chocolate	1 oz	28 g
	Chocolate ice cream	Half of a cup	100 g or 112 ml
	French fries	1 small or 3 oz	84 g
	Kidney beans	Half of a cup	93 g or 112 ml
	Oat ring cereal	1 cup	30 g or 224 ml
	Pizza	Quarter of 12 inch pie	130 g or quarter of 30 cm pie
	Potato	Half of a cup	78 g or 112 ml
	Rice bran	2 tablespoons	15 g or 30 ml
	Soy nuts cereal	1 cup	40 g or 224 ml
	Tahini	2 tablespoons	32 g or 30 ml
	Tofu	4 oz	113 g
	Veal (cutlets)	4 oz	113 g
	Wheat bran cereal	Half of a cup	31 g or 112 ml
	Yeast products (pastes, brewers, vegemite, marmite)	1 teaspoon	5 g or 5 ml

(continued)

Table 17.2 (continued)

Instructions for low-cobalt diet[a]			
Points	Food	Serving size–American	Serving size–metric
2	Alfalfa	1 oz	28 g
	Almonds	1 oz	28 g
	Brownies	1 brownie or 3 × 1 × 1 inch	24 g or 7.5 × 2.5 × 2.5 cm
	Cantaloupe	Half of a cup	80 g or 112 g
	Chicken TV dinner	Half of a dinner or 5.5 oz	154 g
	Chocolate pudding	Quarter of a cup	70 g or 66 ml
	Chocolate syrup	1 tablespoon	16 g or 15 ml
	Crisped rice cereal	1 cup	33 g or 224 ml
	Fruit flavoured cereal	1 cup	30 g or 224 ml
	Ground beef (hamburger patty, Meatloaf)	4 oz	113 g
	Lentils	2 tablespoons	13 g or 30 ml
	Multivitamin	1 tablet	1.5 g
	Navy bean	Half of a cup	93 g or 112 ml
	Nutrigrain bar	1 bar or 1.3 oz	37 g
	Oysters	3 oz	84 g
	Peas	Half of a cup	73 g or 112 ml
	Pepitas	1 oz	28 g
	Prune juice	1 cup	240 g or 224 ml
	Pumpkin	Half of a cup	58 g or 112 ml
	Raisin bran cereal	Half of a cup	30 g or 112 ml
	Red wine	1 cup	240 g or 224 ml
	Shrimp	3 oz	84 g
	Strawberries	Half of a cup	72 g or 112 ml
	Tomato juice	1 cup	240 g or 224 ml
	Walnuts	1 oz	28 g

Table 17.2 (continued)

Instructions for low-cobalt diet[a]			
Points	Food	Serving size–American	Serving size–metric
1	Apple juice	1 cup	240 g or 224 ml
	Apricots	1 fruit or 1.4 oz	38 g
	Asparagus	Half of a cup	67 g or 112 ml
	Avocado	Quarter of a fruit or 2.2 oz	60.5 g
	Bagel	1 bagel or 4.3 oz	120 g
	Beef (steak, rump, chuck, roast, sirloin, round)	4 oz	113 g
	Beef bouillon soup	1 cup	240 g or 224 ml
	Beef taco	1 taco or 3.6 oz	100 g
	Breakfast sandwich (egg, cheese, ham)	1 sandwich or 5 oz	139 g
	Broccoli	Half of a cup	44 g or 112 ml
	Cashews	1 oz	28 g
	Chicken noodle casserole	4 oz	113 g
	Chicken noodle soup	1 cup	240 g or 224 ml
	Chocolate chip cookies	1 cookie or 0.5 oz	14 g
	Cod/haddock fillet	4 oz	113 g
	English muffin	1 muffin or 2 oz	57 g
	Fish sticks and patties	4 oz	113 g
	Granola cereal	Half of a cup	30 g or 112 ml
	Grape juice	1 cup	240 g or 224 ml
	Green beans	Half of a cup	55 g or 112 ml
	Instant mashed potatoes	Half of a cup	105 g or 112 ml
	Lima beans	Half of a cup	55 g or 112 ml
	Multigrain/whole wheat/cracked wheat bread	1 slice or 1.5 oz	43 g
	Mushroom soup	1 cup	240 g or 224 ml
	Oat bran cereal	Half of a cup	35 g or 112 ml
	Onion rings	1 small or 3 oz	84 g
	Peanuts	1 oz	28 g
	Pears	Half of a fruit or 3.2 oz	90 g
	Pecans	1 oz	28 g
	Potato chips	1 oz	28 g
	Prunes	Half of a cup	85 g or 112 ml
	Rye bread	1 slice	37 g
	Salisbury steak TV dinner	Half of a dinner or 6.5 oz	182 g
	Soy sausage	2- to 4-inch links or 1.2 oz	2- to 10-cm links or 34 g
	Stuffed green peppers	Half of a stuffed pepper or 4 oz	110 g
	Sweet potato	Half of a cup	78 g or 112 ml
	Tempeh	4 oz	113 g
	Turkey TV dinner	Half of a dinner or 6 oz	165 g
	Wholemeal flour	Quarter of a cup	30 g or 66 ml
	Squash	Half of a cup	57 g or 112 ml

[a]Limit daily intake to no more than 12 points per day. Amount needed to induce flare may also depend on smoking status and environmental levels in air, soil, and water (i.e. living near industry) (3). A multivitamin counts as 2 points

17.8 Conclusion

There is an enormous body of published work and clinical experience supporting the role of dietary nickel, chromium, and cobalt in cases of systemic contact dermatitis, especially vesicular hand eczema. Reliable data exist for the content of these elements in various foods, along with evidence that avoidance of foods high in the relevant metal leads to improvement in many patients. It is incumbent on those managing patients with vesicular hand dermatitis to consider the potential role of dietary metal as a causative factor, patch test these patients, and implement dietary avoidance in those with positive patch tests.

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18 Prevention of Metal Exposure: Chelating Agents and Barrier Creams

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18.1 Introduction

Metals are a group of elements which are ubiquitous in modern life. They are used in the fields of cosmetics, water purification, medicine, paint, food products, pesticides, and almost innumerable others. As the use of metals has increased in recent decades, so has human exposure to these elements. Metals such as mercury, lead, arsenic, nickel, and others have been implicated in negatively affecting human homeostasis by causing chronic inflammatory diseases, among other serious conditions. Both acute and chronic metal toxicity in vital organs could arise from local or systemic exposure to numerous metals (Fig. 18.1). Although some metals have health benefits, overaccumulation of metals in body tissues can result in deleterious, toxic effects. Most exposure to metals occurs via cutaneous, inhalation, or oral routes [1, 2]. At the highest risk of negative effects of exposure are pregnant women and children [3, 4]. To ameliorate or prevent the toxic effects of metals, chelating agents and barrier creams are used widely in medical practice today. In this chapter, we will discuss preventing metal toxicity from overexposure via chelation therapy and skin barrier creams. This chapter focuses on strategies to scavenge nickel and other metal ions, aside from the application of occlusive agents, which can broadly block exposure of many agents including nickel, while typically reducing the skin's ability to breathe.

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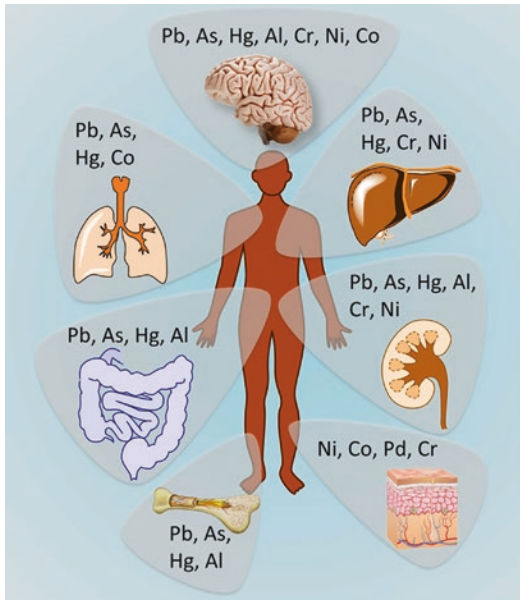


Fig. 18.1 Exposure to a wide variety of metal ions can cause acute and/or chronic organ toxicity

18.2 Chelation Therapy and Chelating Agents

Chelation therapy is an effective way of removing metal ions from the body via the systemic administration of chelating agents. The term "chelation" comes from the Greek word "chelos," meaning claw. Chelating agents are ligands which form metal ion-ligand complexes. The agents sequester metal ions by specifically and non-covalently forming ringlike complexes around the metal with one or more organic (and to a lesser extent, inorganic) molecules.

Chelating agents (used interchangeably with the term ligand(s) here) are classified according to the number of binding groups which can bind the target metal ion at the same time. For example, a molecule with two binding sites is bidentate, a molecule with three binding sites is tridentate, and so on. Thus, the stoichiometry of the complex formed can only be determined through denticity of the chelator. In general, hexadentate ligands are preferred as they form entropically driven, uniform ligand-metal ion complexes with constant stoichiometry (usually 1:1). Conversely, chelating agents with less denticity can have numerous ligand-metal ion geometries, whose speciation pattern depends on both total ligand concentration and metal to ligand ratio.

An optimal chelating agent must possess the following characteristics: (1) have strong binding affinity to metals which form stable complexes that are less toxic than the metal alone, (2) have high aqueous solubility, (3) have chelating complex stability at a wide range of pH, (4) are resistant to chemical transformation, and (5) can readily enter the tissues where the metal is present.

The formation stability constant is an important parameter to consider for any chelating agent-metal ion complex, typically written as "$M_xL_yH_z$" (where M is metal, L is ligand and H is hydrogen). The formation stability constant describes the formation equilibrium of ligand-metal ion complex between fully deprotonated ligand and the metal ions, $xM + yL + zH = M_xL_yH_z$. However, this constant is not always applicable under in vivo conditions. Ligands at physiological pH have metal ions *and* protons simultaneously competing for binding sites. Thus, the formation stability constant does not account for ligand binding to protons, and the comparative efficiency between different chelating agents cannot be studied on the basis of this constant alone. As a result, numerous methods have been developed to accurately compare chelating agents under physiological conditions [5].

An ideal chelating agent has multiple orders of magnitude of selectivity for the target metal ion species relative to other ionized species in the body tissue. This is described by a ligand-metal ion stability constant for other ionized species.

Both the selectivity and stability of chelating agents depend on the hard/soft character of the coordination groups in ligands and free metal ions [6]. These characteristics play an important role in the design of efficient chelating groups. For example, the soft and borderline soft ions Pb^{2+}, Hg^{2+}, Cd^{2+}, and As^{3+} are effectively complexed with ligands containing thiolates and amines in their binding domains [7].

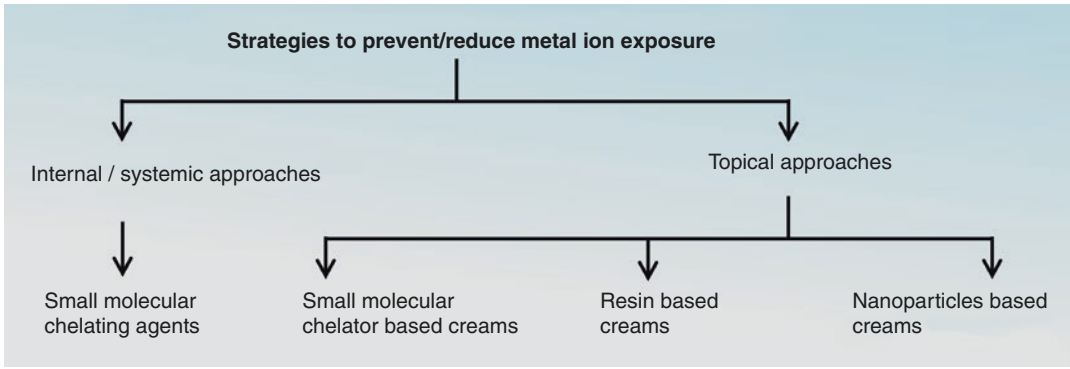


Fig. 18.2 Summary of strategies that have been developed to prevent or reduce metal ion exposure

It is also important to understand the pharmacokinetics of chelating agents to ensure they reach the tissues which contain the toxic metal ions. Specifically, chelating agents can be covalently or non-covalently bound to macromolecules, such as the plasma proteins albumin and transferrin. This non-specific binding can reduce bioavailability and lead to differences in metal binding kinetics. Moreover, several metabolic transformations such as acetylation, glucuronidation, and disulfide bond formation (between chelators and amino acids which contain thiol groups) can further reduce bioavailability. As a result of these transformations, chelating agents can become toxic or lose activity. Hence, resistance toward metabolic transformation is an important parameter to consider while evaluating chelating agents. Chelating agents can also form complexes with low-molecular-weight organic compounds like citrate ions and other metal ion species found in the tissue, such as aluminum, chromium, and palladium, although these complexes form slowly. When considering the duration of chelation therapy, it is vital to account for the following equilibria: (1) the equilibrium between the intracellular and extracellular concentration of the target metal ion, (2) the equilibrium between the intracellular and extracellular concentration of the chelating agent, (3) the equilibrium between a freely circulating chelating agent and the chelating agent in complex with an endogenous molecule, (4) the equilibrium between freely circulating target metal ion species and target metal ion species which are in complex with an endogenous molecule, and (5) the equilibrium between metals in complex with a chelating agent and metals bound to endogenous molecules [8, 9].

Numerous chelating agents have been developed to reduce toxic metal exposure. The routes of administration of these agents can be categorized as internal/systemic and topical. A detailed classification of these strategies is described in Fig. 18.2.

18.3 Strategies to Prevent/Reduce Metal Ion Exposure

18.3.1 Internal/Systemic Approaches

18.3.1.1 Small Molecule-Based Chelating Agents

Polyamino-Polycarboxylic Acid Derivatives

Calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) (Fig. 18.3) is an FDA-approved synthetic polyamino-polycarboxylic acid used to treat lead poisoning in children. It has been in use since 1950 [10]. Pb-EDTA complex has a higher stability constant than Ca-EDTA. Thus, in the $CaNa_2EDTA$ complex, the calcium ion is readily replaced by lead, and the more stable complex,

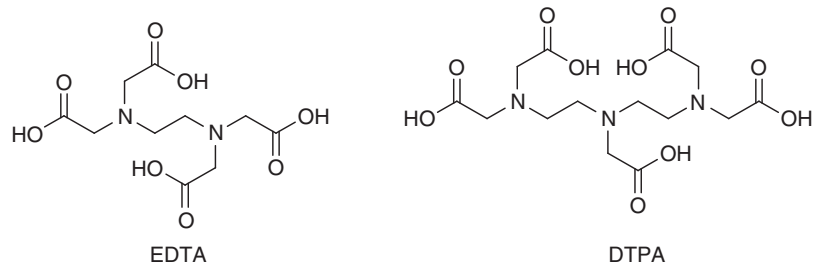


Fig. 18.3 Chemical structure of ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA)

$PbNa_2EDTA$, is formed. $CaNa_2EDTA$ is administered as an intravenous (IV) infusion because intestinal absorption is very low (<5%).

The elimination half-life of $CaNa_2EDTA$ is between 1.4 and 3 h, and all of the ligand is excreted within 24 h of administration [11]. Prolonged use of this chelation therapy can cause depletion of essential metals, especially Zn, Cu, and Mn [12].

Calcium trisodium diethylenetriaminepentaacetic acid ($CaNa_3DTPA$) (Fig. 18.3) is a chemical analog of EDTA and has a higher stability constant than EDTA for a majority of metal ions, including cobalt, zinc, and cadmium [13, 14]. Like EDTA, DTPA has low intestinal absorption and can also deplete zinc from the body. However, zinc depletion from both EDTA and DTPA can be overcome by dietary supplementation of zinc salts. Both EDTA and DTPA are well tolerated by patients, and most adverse events are minor. Adverse events include generalized symptoms such as nausea, diarrhea, and vomiting [15]. DTPA has also been used to eliminate plutonium and other transuranic elements such as californium, curium, and americium from systemic circulation [16]. Ca-DTPA and Zn-DTPA can be used for the chelation of plutonium in humans, though this therapy requires repeated administration over several weeks. DTPA salts exhibit good decorporation efficacy for actinides that are present in extracellular fluids, as DTPA has poor cell membrane permeability. To improve decorporation in the case of radionuclide exposure and because repeated administration is required, early administration of Ca-DTPA or Zn-DTPA after exposure is key to effective treatment when radionuclides are present in extracellular fluids [17].

To increase the cell permeability of DTPA, a lipophilic derivative called "Puchel" was synthesized. This molecule is a chemical analog of DTPA with two n-decane moieties covalently attached [18]. Puchel reduced plutonium concentrations from the liver when injected intravenously [18]. While the lipophilic derivative of DTPA accelerated plutonium clearance from the lungs after inhalation of plutonium and Puchel sequentially, inhalation therapy with Puchel was not effective in reducing the level of plutonium in the liver when compared to inhaled DTPA [19, 20]. Furthermore, in animal inhalation studies, lung inflammation and liver damage were observed in groups receiving treatment both weekly and monthly. As a result, this derivative was abandoned for medical use [21].

Other lipophilic derivatives of DTPA have been developed by varying the chain length of alkyl substituents. Oral administration of these derivatives showed improvement in decorporation of plutonium when measured by neutron-induced autoradiography when compared to DTPA [22, 23]. The best of these derivatives was docosyltriethylene tetramine pentaacetic acid (C22TT). C22TT reduced the cytosolic concentration of plutonium in liver cells in vitro [24]. In vivo rat studies were performed by injecting 239-Pu and 241-Am 2 weeks prior to oral administration of C22TT. Treatment with C22TT showed significant reduction of plutonium in soft tissues, bones, and the bone marrow after 30 days. Neutron-induced autoradiography studies showed that C22TT significantly inhibits the redistribution of plutonium in skeletal tissues after oral administration of C22TT. C22TT chelators are well absorbed

through the intestine and eliminated through fecal excretion in the complexed as well as uncomplexed state [25].

The transuranic radionuclide Americium-241 (241-Am) is found in abundance as a by-product of plutonium processing during nuclear power and nuclear weapon production. Similarly to transuranic elements like plutonium, 241-Am also poses serious health hazards to humans. In order to decorporate 241-Am, a prodrug of DTPA was developed in 2014 using a penta-ethyl ester DTPA conjugate [26]. Pharmacokinetic and biodistribution studies conducted in rodents demonstrated sustained plasma concentration with low clearance. This compound exhibited 19% higher urinary excretion of 241-Am than control after exposing the rats to aerosolized 241-Am.

In another approach, nanotechnology delivery methods were used to increase the oral bioavailability of DTPA. This approach used nanoscale particles of DTPA which were encapsulated with zinc acetate and GI permeability enhancing compounds within enteric-coated capsules [27, 28]. These capsules, under development by *Nanotherapeutics*, have shown a significant improvement in DTPA bioavailability in dogs and efficacy for decorporation of 241-Am after oral administration of the DTPA particles. The efficacy of these capsules for decorporation was similar to IV administration of Zn-DTPA when tested in the same model [28]. In 2011, *Nanotherapeutics* obtained orphan drug status for NanoDTPA capsules and approval from the US FDA to treat radiation exposure.

Thiol-Based Chelating Agents (BAL, DMSA, DMPS, D-Penicillamine)

During World War II, 2,3-dimercaprol (BAL) was developed as a chelating agent by British biochemists at Oxford University. BAL has been used clinically for arsenic, cadmium, and mercury poisoning since 1949 [29]. Chemically, BAL is a three-carbon chain with two sulfhydryl (−SH) groups and a hydroxyl (−OH) group (Fig. 18.4). It is an oily, colorless liquid with a pungent odor. It is used clinically for lewisite (an organoarsenic compound) poisoning and acts by forming a stable five-member ring complex with the arsenic moiety of lewisite (Fig. 18.4). BAL is most effective when administered immediately after exposure to lewisite. BAL is also an efficient antidote for mercury poisoning. However, the metals are rapidly mobilized systemically after BAL administration. As a result of this mobilization, significant redistribution of mercury and arsenic compounds has been observed. Subsequently, these metals can then be deposited into the soft tissue, such as the brain [30, 31]. BAL can also be used for cadmium exposure, and previous reports have demonstrated improved urinary excretion of cadmium after BAL administration. However, renal cadmium concentration also increased. BAL's oily composition and short half-life render oral administration unfeasible, and intramuscular administration is painful. BAL is also known to cause allergic reactions in some patients [32].

Dimercaptosuccinic acid (DMSA) is a chemical analog of BAL which exhibits superior effi-

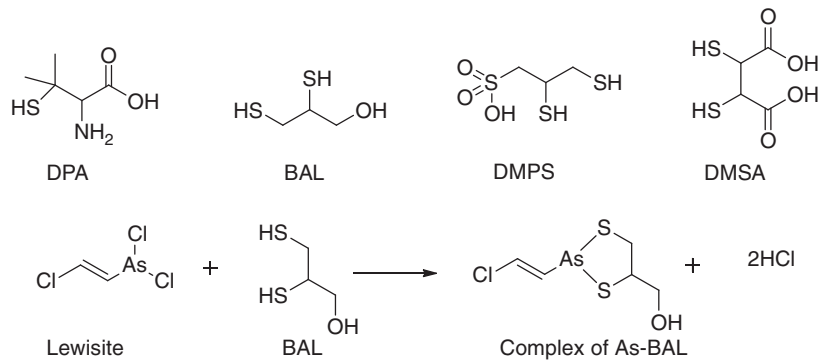


Fig. 18.4 Chemical structures of thiol-based chelators, such as D-penicillamine (DPA), 2,3-dimercaprol (BAL), 2,3-dimercaptopropane-1-sulfonate (DMPS), and 2,3 dimercaptosuccinic acid (DMSA) (*top*) and the BAL-lewisite ligand complex formation (*bottom*)

cacy for heavy metal poisoning compared to BAL [33]. DMSA is a hydrophilic compound and is absorbed in the gastrointestinal tract, which permits oral administration. Formulation of DMSA is much easier than BAL, despite their chemical similarities, which provides a major advantage to this compound for clinical applications [33]. DMSA is prepared as a capsule coated with citric acid solution and lemon oil (to disguise the unpleasant odor of DMSA). DMSA covalently binds to the cysteine group of plasma albumin via one of the –SH groups on the DMSA molecule. The other –SH moiety on DMSA is left unbound for non-covalent metal coordination [34]. DMSA is one of the least toxic dithiol chelators and has a wide therapeutic window [35]. Moreover, DMSA does not result in significant loss of essential metal ions such as Zn, Mg, Fe, and Ca. To improve cell permeability while retaining chelating properties, ester derivatives were synthesized, including monoisoamyl DMSA (MiADMSA) [36, 37], monomethyl DMSA (MmDMSA), and monocyclohexyl DMSA (McHDMSA) [38]. Monoester DMSA compounds have demonstrated higher efficacy for chelation of toxic metal ions such as arsenic, lead, and cadmium while demonstrating less toxicity than DMSA [38]. Among dithiol compounds, DMSA has shown the highest efficacy for chelating arsenic ions while exhibiting minimal toxicity [39]. Despite these favorable characteristics, DMSA does have some drawbacks. For example, DMSA can result in altered copper metabolism and extracellular redistribution of heavy metals in the soft tissue, such as the brain [40].

Sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) is an analog of 2,3-dimercaprol (BAL) consisting of dithiol and sulfonic acid groups. DMPS is less efficient than $CaNa_2EDTA$ and DMSA at lead and arsenic chelation [41]. However, it has shown increased efficacy for reducing systemic mercury concentrations after mercury poisoning [42, 43]. DMPS is registered in Germany as a drug for treating mercury poisoning; however, it is not approved in the United States. DMPS is hydrophilic, is distributed extracellularly, and exhibits poor cell membrane permeability. The major advantage of DMPS relative to other compounds is that it does not redistribute mercury to the brain [44].

3-mercapto-D-valine, also known as D-penicillamine (DPA), is a degradation product of penicillin and consists of the amino acid valine with a sulfhydryl group. Only the D-isomer of this compound is used for chelation of metals such as lead, mercury, and copper. Interestingly, L-penicillamine causes optic neuritis and inhibits vitamin B_6 activity [45]. DPA is primarily used for eliminating excess copper from patients with Wilson's disease, a rare, inherited copper storage disorder [46]. Mechanistic studies found that the chelating properties of DPA alone are not sufficient to mobilize toxic copper in patients. Specifically, DPA undergoes a process known as reductive chelation in the presence of copper ions, where Cu^{2+} is converted into Cu^{1+} as the chelator is oxidized [47, 48]. Upon oral administration, DPA is well absorbed in the gastrointestinal tract and is largely concentrated extracellularly after absorption. The drug is eliminated from the body through the urine, and elimination half-life ranges from 1 to 7 h. DPA reaches peak plasma concentration between 1 and 4 h after oral administration. DPA can result in serious complications, such as thrombocytopenia and leukocytopenia (5–15% of patients). DPA also has ulcerogenic activity [49, 50].

Compounds containing dithiol groups can also act as oxygen radical scavengers. This provides a mechanism to reduce oxidative stress induced by heavy metals inside the cells via lipid peroxidation inhibition.

Triethylenetetramine Dihydrochloride

Triethylenetetramine (Trien) is a highly selective copper-chelating agent (log K = 20.1) and results in urinary copper excretion [11]. Trien has few side effects after oral administration, although mild sideroblastic anemia and gastrointestinal side effects have been reported with rare frequency [11]. Trien is a positively charged compound (Fig. 18.5), and is poorly absorbed through the gastrointestinal tract. Only 5–18% of Trien is absorbed systemically. Trien is extensively metabolized, and two major metabolites of Trien have been identified: N^1-acetyltriethylenetriaamine and N^1,N^{10}-diacetyltriethylenetriaamine. N^1-acetyltriethylenetriaamine is predominantly responsible for copper chelation and excretion [51, 52].

Ammonium Tetrathiomolybdate

The tetrathiomolybdate ion (MoS_4^{2-}) of ammonium tetrathiomolybdate (TM), $H_8N_2MoS_4$ (Fig. 18.5), forms complexes between the molybdenum species, copper, and proteins, which reduces free serum copper levels. These combined TM-albumin-copper complexes are metabolized in the liver and excreted in bile [53, 54]. TM was first recognized as an anti-copper agent in 1986 by Walshe and colleagues when it was used in two patients with Wilson's disease who could not tolerate either D-penicillamine or Trien [55]. Administration of TM preserves neurological function in patients with Wilson's disease better than D-penicillamine or Trien [56]. As of 2016, TM is not approved for use by the FDA due to its two major side effects: (1) depletion of bone marrow cells (as they require copper for proliferation), which leads to leukopenia with anemia, and (2) elevation of liver transaminase levels such as alanine transaminase (ALT) and aspartate transaminase (AST) up to three to four times the upper limit of normal [57].

Nitrilotriacetic Acid (NTA)

Nitrilotriacetic acid (NTA) is similar in structure to EDTA (Figs. 18.5 and 18.3, respectively). NTA is used to chelate metal ions such as Ni^{2+}, Ca^{2+}, Cu^{2+}, or Fe^{3+} and, unlike EDTA, is biodegradable. NTA is available as either a sodium salt (Na_3NTA) or an iron salt (FeNTA) [58]. Nickel deposition in vital organs and at the site of contact poses serious health hazards to industrial workers. The chelators BAL and sodium diethyldithiocarbamate (DDC) are able to form stable complexes with nickel but have shown limited success in ameliorating nickel poisoning in animal models [59]. In a study, six chelating agents, NTA, EDTA, DTPA, 1,2-cyclohexylene dinitrilotetraacetic acid (CDTA), 3,6-dioxaoctamethylene dinitrilotetraacetic acid (DDTA), and sodium diethyldithiocarbamate (DDC), were screened for their abilities to reduce the toxic burden in rats after exposure to nickel sulfate. NTA showed the best efficacy for eliminating nickel within subcellular fractions of the liver, kidney, and blood corpuscles after exposure to nickel sulfate [59]. Intraperitoneally administered NTA can also remove nickel from brain, heart, kidney, and liver tissue in rats. Despite the efficacy of NTA, adenocarcinoma was observed in animal models in a dose-dependent fashion, and tumor formation was observed at higher doses in the same model [60]. Administration of Na_3NTA resulted in the depletion of the metals Zn, Ca, and Mn and caused toxicity [61]. Furthermore, FeNTA causes iron overload and lipid peroxidation and is genotoxic [62, 63].

Desferrioxamine

Desferrioxamine, also called deferoxamine (DFO) (Fig. 18.6), is a trihydroxamic acid

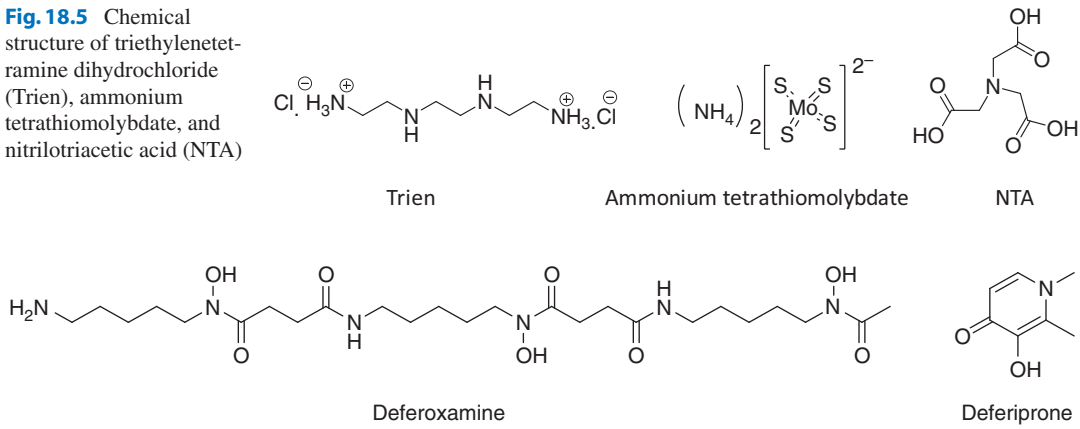


Fig. 18.5 Chemical structure of triethylenetetramine dihydrochloride (Trien), ammonium tetrathiomolybdate, and nitrilotriacetic acid (NTA)

Fig. 18.6 Chemical structures of deferoxamine (DFO) and deferiprone

siderophore produced from *Streptomyces pilosus*. DFO was initially discovered as an inhibitor of the antibiotic ferrimycin and was later identified as an iron chelator [64]. The chemical structure of DFO is a linear chain consisting of three residues of 1-amino-5-*N*-hydroxy aminopentane, two succinic acid groups and one acetic acid group. DFO has the highest binding affinity for trivalent iron. It has been used for treating iron-related diseases, such as thalassemia. DFO can also be used to chelate aluminum and has been applied to treat aluminum poisoning associated with chronic renal dialysis [65]. This chelating agent is poorly absorbed in the gastrointestinal tract and does not readily penetrate cell membranes. It is administered through intravenous injection or infusion. The half-life of DFO is very short, just 5 to 10 min, so therapy is typically a prolonged infusion over 9–12 h [66]. DFO forms complexes with iron to generate ferrioxamine, which is rapidly excreted through the kidney and feces [67, 68].

Deferiprone

Deferiprone, 3-hydroxy-1,2-dimethylpyridin-4(1H)-one, which is also known as ferriprox (Fig. 18.6), was synthesized in 1982 by Robert Hider and his colleagues at Essex University [69]. It was the first oral chelating agent available for clinical use for Fe^{3+}. It is used as an alternative to DFO in approximately 50 countries. Deferiprone is used primarily on patients with thalassemia to balance iron and to maintain negative iron balance in iron overload transfusion patients [70]. Instead of a constant infusion, it is administered two or three times per day for patients experiencing iron overload. Unlike DFO, deferiprone can penetrate the cell membrane and can chelate intracellular iron. Deferiprone is a bidentate ligand, which forms complexes with Fe^{3+} in a 3:1 ratio. It has the capability to remove Fe^{3+} from the core of ferritin, an endogenous iron-containing protein. Deferiprone can also liberate iron from hemosiderin, lactoferrin, and transferrin [71–73]. The major metabolites of deferiprone are glucuronide conjugates, which are excreted mainly through the kidneys (70%) and feces (30%) [74].

Exjade

Exjade, *N*-substituted bis-hydroxyphenyl-triazole 4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl] benzoic acid, which is also known as deferasirox (Fig. 18.7), is a tridentate ligand with high affinity and specificity for iron (log K_1 = 10.6, log K_2 = 9.0, log K_3 = 3.7). The ligand has three polar interaction sites which bind with iron in a 2:1 ratio, where two molecules of deferasirox are required to form a stable complex with one Fe^{3+} ion.

Clinical trials were conducted with male patients (>18 years of age) with transfusion-dependent β-thalassemia. Patients received a single oral dose of deferasirox ranging from 2.5 mg/kg to 80 mg/kg to determine the safety, tolerability, and pharmacokinetics [75]. Twenty-four patients were divided into three groups (eight patients in each group) and given two oral doses 7 weeks apart. Administration of deferasirox was started with the lower dose, and the dose was then increased according to treatment group (group 1, 2.5 mg/kg and 20 mg/kg; group 2, 2.5 and 40 mg/kg; group 3, 10 and 80 mg/kg; and a placebo group). None of the patients demonstrated severe adverse effects in any group. However, mild adverse effects were reported. Headache occurred in four patients in the 2.5 mg/kg group, one in the 20 mg/kg group,

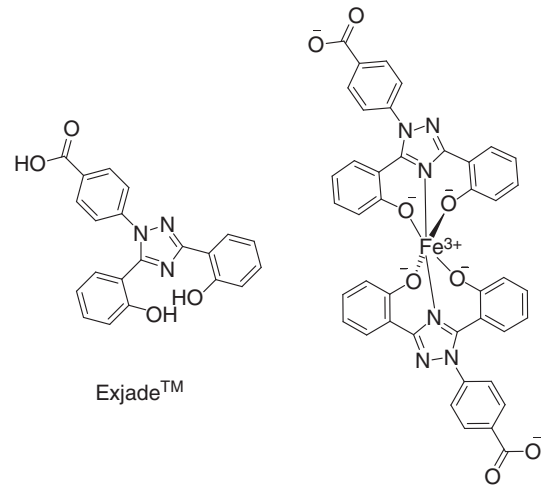


Fig. 18.7 Chemical structure of Exjade (deferasirox) and chelation structure with Fe^{3+} ion in 2:1 ratio

and one in the placebo group. Nausea and diarrhea were reported only in patients in the 80 mg/kg dose. Thus, deferasirox has good tolerability and is safe in doses up to 80 mg/kg/day, while the normal dose is 20–30 mg/kg/day. The total body iron elimination rate in patients treated with deferasirox was between 7.7 and 28.5 mg Fe/day, similar to patients treated with deferoxamine, the current standard among iron chelators [75]. The compound has a half-life of 11–19 h, which permits once-daily dosing. Iron is eliminated almost quantitatively in the feces and is not redistributed into other tissues of the body. Indeed, the net iron excretion is linearly related to the administered dose of the chelator. Deferasirox was the second oral iron chelator to be approved by the FDA.

Prussian Blue

Prussian blue, also known as Radiogardase, is ferric hexacyanoferrate ($Fe_4[Fe(CN)_6]_{3)}$ (Fig. 18.8). Since 1960, it has been used for the treatment of radioactive cesium and nonradioactive thallium exposure. Prussian blue binds radioactive cesium and nonradioactive thallium through ion exchange, absorption, and mechanical trapping within the crystal structure. Insoluble Prussian blue has high affinity for soft metal ions and exploits ion exchange properties to immobilize cesium and thallium in the gastrointestinal tract to inhibit systemic absorption [76]. After binding to the radioactive cesium, Prussian blue reduces the biological half-life of cesium from 110 days to 30 days, and the biological half-life of thallium is reduced from 8 days to 3 days. The reduction in biological half-life is the key to the efficacy of Prussian blue, as temporal exposure to radioactivity is decreased almost fourfold. Depending on the method of crystallization, Prussian blue can exhibit different chelating properties, and its clinical use has been restricted to gastrointestinal exposure of cesium and thallium. No serious adverse events were found in rats after oral administration of 137-Cs when 100 mg Prussian blue was administered by gastric intubation for 11 days. Furthermore, no side effects or growth impairment was observed in the same group of rats when 1% PB was given for 120 days in normal feed. Moreover, no toxic effects were observed in male Sprague-Dawley rats after their drinking water was supplemented with Prussian blue at 23 and 226 mg/kg/day for 60 days. Two human volunteers who were exposed to radiation at the site of the Chernobyl nuclear disaster were exposed to Prussian blue at 3 g/day for 20 days. As a result, the biological half-life of 137-Cs was reduced by 60–70% without any side effects, except for minor constipation [77].

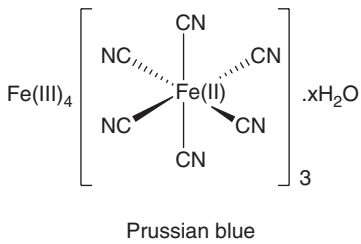
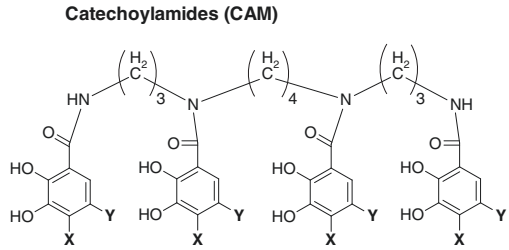


Fig. 18.8 Chemical structure of Prussian blue ($Fe_4[Fe(CN)_6]_3$

Siderophores

Siderophores are molecules which transport iron in microorganisms. These compounds are multidentate ligands with a centrally located metal binding site. Examples include desferrithiocin, a natural product tridentate chelator, enterobactin analogs which contain catecholamine (CAM) moieties, and hydroxypyridones (HOPO) (Fig. 18.9). Siderophores can be used as chelators for radioactive actinides, including uranium and plutonium, as they are similar in size to iron. Desferrithiocin and its analogs were tested for their ability to reduce the distribution of uranium in rats exposed to the metal [78]. Out of ten analogs of desferrithiocin, two containing polyether moieties resulted in increased excretion of uranium, reduced nephrotoxicity, reduced renal uranium content, and decreased metal concentration in the bone [78]. However, these molecules were not continued for further clinical development.

Among the CAM family of chelators, 3,4,3-LI-CAM (C) is the most extensively studied. 3,4,3-LI-CAM (C) exhibited high decorporation activity relative to DTPA for some lipophilic forms of Pu, such as Pu-TBP [79–81]. Tributyl phosphate (TBP) has been used as a versatile extracting solvent during reprocessing of spent



Abbreviation	X	Y	IUPAC name
3,4,3-LI-CAM (C)	-COOH	-H	N^1,N^5,N^{10},N^{14}-tetrakis(2,3-dihydroxy-4-carboxybenzoyl) tetraazatetradecane
3,4,3-LI-CAM (S)	-H	$-SO_3H$	N^1,N^5,N^{10},N^{14}-tetrakis(2,3-dihydroxy-5-sulphobenzoyl) tetraazatetradecane

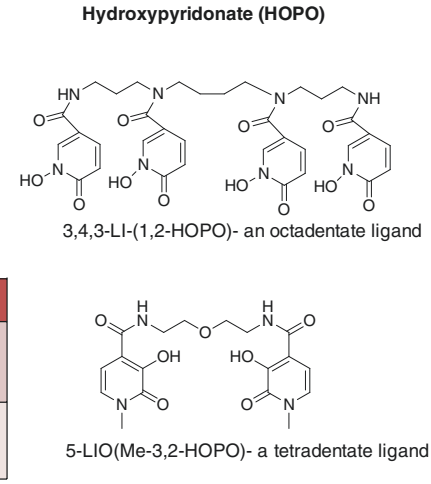


Fig. 18.9 Chemical structures of catecholamines carboxylate CAM(C), sulfonate CAM(S), and hydroxypyridonates (HOPO)

nuclear fuel. During extraction, TBP forms a complex with plutonium, Pu-TBP, which is difficult to handle. 3,4,3-LI-CAM (C) is the only chelator which can effectively bind neptunium, although the systemic reduction of neptunium is limited to 50% of the administered amount [82]. However, clinical use of 3,4,3-LI-CAM (C) was never pursued because of high renal retention of transuranic elements [83, 84].

The hydroxypyridonate (HOPO) chelators consist of either tetradentate or octadentate ligands. Within the HOPO family, 3,4,3-LI(1,2-HOPO) and 5-LIO(Me-3,2-HOPO) are the most efficient chelators [85–88]. Additionally, 3,4,3-LI(1,2-HOPO) is able to remove a significant amount of both Pu and Am from the bone [89]. Immediate intramuscular injection of 3,4,3-LI(1,2-HOPO) after intramuscular injection of uranyl nitrate increased urinary concentration of uranium and reduced the retention of uranium in the femur and kidney [90]. Timely administration of 3,4,3-LI(1,2-HOPO) is important. If 3,4,3-LI(1,2-HOPO) administration is delayed by 30 min after exposure to uranium, scavenging efficacy is reduced in the bone. An et al. have shown the successful removal of 238-Pu citrate (aqueous solution, orally administered) from mice via 3,4,3-LI(1,2-HOPO) chelation, although variable efficacy was noted between males and females [91]. There was slight reduction of the tissue burden of plutonium in male animals (~1.5-fold) as compared to female animals. Oral delivery of 3,4,3- LI(1,2-HOPO) was considered to be an effective chelator for removal of Pu [92]. Additionally, the oral administration of the combination of 3,4,3- LI(1,2-HOPO) and 5-LIO(Me-3,2-HOPO) showed a higher efficacy than DTPA alone in removing actinides from the skeleton, body, and liver. Moreover, the combination was found to be nontoxic up to 1 mM on human primary cells derived from the lung, liver, and kidney (in vitro) and well tolerated in rats when orally administered daily at high doses (100 μmol/kg per day) for 28 days and showed no signs of genotoxicity [93].

However, HOPO-based compounds are not typically permeable across the GI tract. A bidirectional permeability study showed that 3,4,3-LI(1,2-HOPO) is not permeable across a Caco-2 monolayer, demonstrating the need for improving oral bioavailability across GI cells [94]. To evaluate the pharmacokinetics and biodistribution of HOPO compounds, ^{14}C-labeled 3,4,3-LI(1,2-HOPO) was administered IV, intraperitoneally (i.p.), or orally (p.o.) in mice and rats. In the case of IV and i.p. administration, radiolabeled chelator was rapidly distributed to highly vascularized organs, such as the kidney and liver. Male mice excreted 22% of ^{14}C labelled chelator through the renal pathway compared to female

mice who only excreted 12% of ^{14}C through the renal pathway. The opposite trend was observed in rats, where female rats showed higher renal excretion than males. Thus, the elimination rate of HOPO compounds depended on the animal species and sex. To improve the oral bioavailability, 3,4,3-LI(1,2-HOPO) was formulated with a proprietary permeability enhancer to create 3,4,3-LI(1,2-HOPO), which led to a significant increase in oral bioavailability. This formulation is currently in phase I clinical trials in the United States [95].

Polyphosphonates

Organophosphorus compounds such as 1-hydroxyethane-1,1-diphosphonic acid (HEDP) (Fig. 18.10) are capable of chelating uranium and have been studied for the treatment of radioactive uranium exposure. HEDP has been used in the clinic as Didronel for the inhibition of bone resorption in Paget's disease. HEDP chelates Ca^{2+} ions present in the bone, and the complex formed is highly apoptotic to osteoclast cells when ingested. Apoptosis of osteoclast cells reduces breakdown of the bone tissue, a defining feature of Paget's disease. Several studies have also shown that a single injection of HEDP reduced renal damage and reduced mortality after exposing rats to uranyl nitrate [96–100]. Furthermore, Bozal et al. showed that treatment with HEDP reduced endochondral ossification in mice after oral administration of uranyl acetate at a lethal dose (350 mg/kg) [101]. Moreover, oxygen-dependent erythropoietin production impairment due to uranium exposure was reversed after HEDP administration in adult Wistar female rats [102]. In order to prevent significant topical contamination of uranium through wounds, the chelator HEDP and carballylic amidobisphosphonic acid (CAPBP) were applied as a paste (composed of carboxymethylcellulose hydrocolloids as absorber) on the wounds of rats after 1 hour of contamination with uranium oxide (UO_4). The wounds were made by incision at the hind left leg to deposit UO_4, the tibialis cranialis and gastrocnemius caput muscle were separated, and in some animals, the gastrocnemius caput muscle was incised lengthways (for inter- and intramuscular deposition, respectively, of uranium and chelator). The HEDP- and CAPBP-containing pastes absorbed 30% and 60% of UO_4 when applied after deposition in intramuscular and intermuscular wounds, respectively [103–105]. Recently, a library of bisphosphonates-based chelators has been generated for uranium binding [106]. From the library, 23 bidentate and tridentate chelators bearing bisphosphonates functional groups—which can selectively bind uranium—have been tested in animals. Among them, eleven were able to mobilize uranium from the kidneys and bones. Bidentate bisphosphonates was the most potent agent, and this compound reduced the retention of uranium and enhanced its excretion by 10% [106].

Calixarenes

Calixarenes have been used in the nuclear industry as chelating agents for the selective extraction of trace amounts of actinides such as uranium,

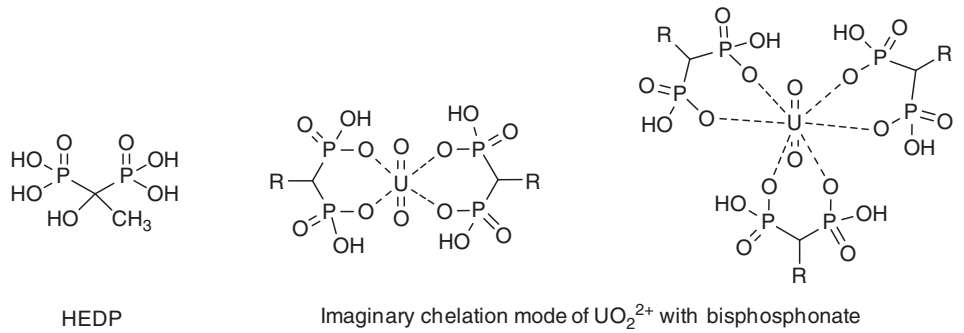


Fig. 18.10 Chemical structures of 1-hydroxyethane 1,1-diphosphonic acid (HEDP) and hypothetical mode of chelation with bisphosphonates

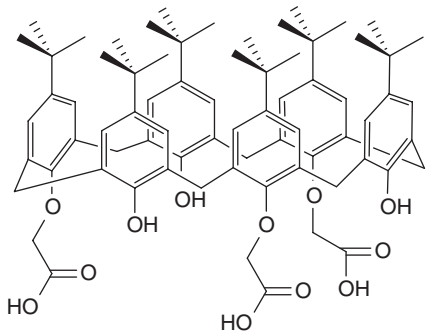


Fig. 18.11 Chemical structure of p-tert-butylcalix[6] arene showing chelating property toward uranium

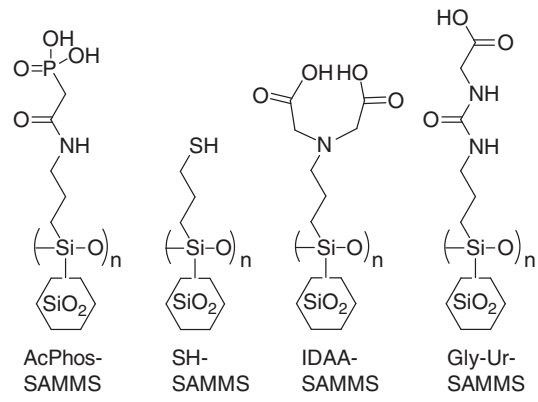


Fig. 18.12 Chemical structures of mesoporous silica nanoparticles functionalized with different organic molecules

plutonium, and americium in biological matrices or environmental samples [107, 108]. The calix[6]arenes have a bucket-like conformation, which is hydrophobic in the center and has functional groups at the periphery. This confirmation favors the binding of metal ions [109]. *p*-tert-butylcalix[6]arene (Fig. 18.11) consists of three carboxylic groups arranged in C3 symmetry with a cone conformation and forms a pseudo-planar hexacoordinate complex with uranium. These complexes exhibit higher affinity and selectivity compared to calix[6]arene, which contains six carboxylic acid groups [109, 110]. There are very few reports on the toxicity of calixarene, and one of the reports claimed that the toxicity of calix[6]arenes and calix[8]arenes functionalized with sulfonate groups is similar to glucose [111]. Sulfonated calix[8]arenes showed a maximum of 30% hemolysis, whereas the sulfonated calix[6] arene analog was nontoxic [112]. However, the toxicity of calixarenes containing carboxylic groups was not evaluated because less toxic molecules, such as 1,3,5-OCH_3-2,4,6-OCH_2COOH-*p*-tert-butylcalix[6]arene, were nontoxic and are better chelators.

18.3.1.2 Silica Nanoparticle-Based Chelating Agents

Functionalized Silica Nanoparticles

Rapidly growing nanotechnologies have offered a new platform to design materials for the diagnosis and treatment of diseases, including the removal of toxic heavy metals. For this purpose, nanomaterials must possess the following characteristic features:

1. Have high affinity to selectively capture metal species even at low concentrations
2. Be nontoxic and biocompatible

Recently, nanoporous silica materials have shown a tenfold greater efficacy for treating heavy metal toxicity (Hg, Pb, Cd) than standard chelating agents (BAL, DMSA, DMPS) [113–115]. Furthermore, as described previously, thiol functional groups impart advantages to molecules for chelating metal ions. Therefore, these two features, nanoporous silica and thiol functionalization, were employed in the development of novel mesoporous silica-based nanomaterials [113, 114]. Thiol-modified nanoporous silica materials (Fig. 18.12) have been tested in vitro and in vivo for the detoxification of heavy metals such as mercury, cadmium, and lead [113]. Self-assembled monolayers on mesoporous supports (SAMMS), also referred to as surface-functionalized nanoporous silica, are covalently linked to mesoporous silica (SiO_2) and cross-linked to organic molecules to generate a dense molecular rug. SAMMS are highly efficient metal sorbents compared to activated carbon or polymer resin-based sorbents [113, 114]. The surface-modified nanoporous silica has a large surface area for the adsorption and desorption of small molecule chelators and metal ions. More importantly,

SAMMS can be engineered to selectively adsorb transition metals, oxometallate anions, heavy metals, actinides, lanthanides, cesium, and thallium [113]. Moreover, these nanoporous silica are hydrothermally stable, and the well-ordered, porous structure on the surface promotes active adsorption of metal ions with high affinity. In addition to thiol modification, acetamide phosphonic acid, glycinylurea, and iminodiacetic acid SAMMS have been studied for metal adsorption [113, 114]. However, thiol-modified SAMMS (SH-SAMMS) possess better metal sorption properties compared to SAMMS modified with other functional groups [114]. Yantasee et al. (2010) showed that SH-SAMMS readily adsorb heavy metals from blood, urine, and other biological samples [113].

Furthermore, it has been shown in rodents that SH-SAMMS delivered orally readily adsorb Hg^{1+}, Cd^{2+}, and Pb^{2+} and do not affect the concentration of other minerals in the blood [114]. Additionally, treating human intestinal epithelial cells in vivo (i.e., Caco-2 cells) with SH-SAMMS showed no cellular damage. The SH-SAMMS were less toxic compared to other surface-modified SAMMS and other chelating agents such as DMSA and DMPS [114]. This evidence supports the theory that thiol-modified mesoporous silica materials are highly efficient adsorbents compared to other SAMMS and chelating agents and that SH-SAMMS do not cause cellular damage when administered orally. SH-SAMMS are good candidates for oral delivery and have the advantage of being nontoxic when used for human therapeutic metal detoxification.

18.3.2 Topical/Barrier Approaches

18.3.2.1 Small Molecular Chelator-Based Barrier Creams

Exposure to nickel via social and occupational exposure is the most common cause of contact dermatitis and affects approximately 10% of the global population [116]. Nickel is in widespread use and can be found in commodities such as jewelry, coins, and fabric. Industrial workers in certain occupations—such as electroplating, a chemical process used during production of glass, enamel, and storage battery production—are continuously exposed to nickel. The continuous exposure to nickel results in an amplified allergic response to the metal in the form of eczema, inflammation, and atopic dermatitis. This is known as nickel sensitization. Nickel sensitization occurs during occupational exposure in industries outside of industrial settings as well and can affect hairdressers, cleaners, money handlers, and jewelers, in addition to metal workers [117]. Over the last 50 years, several substances have been investigated to reduce the symptoms of nickel allergy through chemical chelation of nickel. These molecules have been incorporated into formulations such as barrier creams [118]. These barrier creams shield the skin where the cream is applied from metal exposure, primarily via absorption of the allergen onto the cream instead of the skin. A considerable amount of research has been conducted to develop barrier creams using a broad range of chelating agents. A detailed description of barrier creams containing chelating agents is discussed here.

Ethylenediaminetetraacetic Acid (EDTA)-Based Barrier Cream

EDTA, a polyaminocarboxylic acid, has been widely used as a chelating agent for metal ions. A topical cream has been developed consisting of 15% EDTA and 1% hydrocortisone (a corticosteroid), which was able to partially reduce the severity of allergic reactions in 10 out of 26 nickel-sensitive subjects after a 2-day challenge with coins containing 16% nickel and 84% copper [119, 120]. In a similar study, cream consisting of 10% Na_2H_2EDTA was applied on the hands of nickel-sensitive patients. After 15 min of pretreatment, subjects were exposed to a test patch containing an aqueous nickel sulfate solution (0.01, 0.1, or 1%). Subjects exposed to 0.01% and 0.1% nickel solution after application of the cream had no allergic reaction. In comparison, the severity of the reaction was reduced or eliminated in all but one of the subjects exposed to the 1% solution after pretreatment with the barrier cream. Specificity of the cream toward nickel was suggested when no beneficial effect

was observed in patients who had a chromium allergy and were challenged with chromium exposure [121]. In vitro experiments with a cream consisting of 2% Na_2H_2EDTA and 4% $CaNa_2EDTA$ showed faster binding to Ni^{2+} than any other combination of chelators. Moreover, topical preparations with low pH and 1.8% Na_2H_2EDTA and 5.4% $CaNa_2EDTA$ showed better capacity to detoxify Ni^{2+} than preparations with a high pH [122]. Other investigations into treating nickel-sensitive subjects with EDTA-based chelators showed the antigenic properties of Ni^{2+} were eliminated after chelation. Thus, application of topical EDTA-based chelating agents can reduce the number of positive nickel patch tests over the area where they are applied [123]. The results from the studies carried out with creams consisting of chelating agents provided a foundation for the development of topical creams for clinical use.

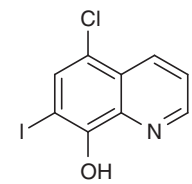
Diethylenetriaminepentaacetic Acid (DTPA)-Based Barrier Cream

DTPA is a polyaminocarboxylic acid similar to EDTA that is an effective chelator of metal ions. DTPA showed markedly superior detoxifying capacity against nickel, cobalt, and chromium compared to EDTA [124]. Considering the advantages of DTPA and that DTPA cream is well tolerated on the skin, a dermal cream has been formulated containing 10% $CaNa_3DTPA$ salt as an oil-in-water emulsion (35% lipid/65% water) to prevent metal exposure [125, 126]. During a clinical study, 28 subjects were exposed to 2.5% nickel sulfate solution (which is higher than the typical amount needed to induce an allergic reaction in sensitive patients), and 28 had no skin reaction. Similarly, out of 19 individuals who were patch tested with cobalt (1% cobalt in an aqueous solution), 18 of them had no reaction to the patch test after pretreatment with the same cream [125]. In another study, 14 patients were exposed to copper, which is only rarely allergenic. Pretreatment with DTPA cream reduced the number of patients with a positive reaction from 13 to 5. Moreover, the severity of the reaction to copper in those five who tested positively after pretreatment was reduced [125]. The cream was tested against palladium- and chromium-sensitized subjects as well but failed to show a significant reduction in preventing hypersensitivity [125].

Clioquinol (5-Chloro-7-iodoquinolin-8-ol)-Based Barrier Cream

Among all the chelating agents, clioquinol (Fig. 18.13) is the most effective ligand for chelating nickel ions. It is currently used to make a cream formulation for nickel dermatitis [120].

To evaluate its capacity to reduce nickel exposure-induced hypersensitivity, 29 nickel-sensitive volunteers were exposed to nickel-containing coins after 48 h of pretreatment with the barrier cream. Subjects were then exposed to nickel and assessed after 24 h. Groups were assigned to receive clioquinol in a paraffin base as pretreatment at concentrations of either 10%, 3%, 1%, or 0.3% [120]. All volunteers receiving 10% and 3% formulations had no reaction at 72 h. Of the patients treated with 1% and 0.3% clioquinol, 20 out of 22 patients and 12 out of 22 patients had no reaction, respectively. As a result, Vioform-HC cream was developed, containing 3% clioquinol and 1% hydrocortisone. Efficacy of Vioform-HC was studied in five people with bilateral earring dermatitis. Vioform-HC was applied on one ear, and 1% hydrocortisone alone was applied on the other ear three times per day, while subjects continued to wear earrings which were known to cause a hypersensitivity reaction. The ear which was treated with Vioform-HC showed inhibition of an allergic reaction in all five individuals. Conversely, the side treated with 1% hydrocortisone developed an allergic reaction. Vioform-HC cream also showed clinical improvement in five patients with bilateral hand eczema caused by



Clioquinol

Fig. 18.13 Chemical structure of clioquinol (5-chloro-7-iodoquinolin-8-ol)

nickel exposure, compared to only two patients who showed improvement after treatment with only 1% hydrocortisone [120].

18.3.2.2 Resin-Based Barrier Creams

Negatively Charged Cationic Exchange Resin-Based Cream

Cationic exchange resins, which consist of negatively charged functional groups (usually sulfonate moieties), have been developed to chelate metal ions. A cationic exchange resin-based ointment, Ivosin RK, consists of a copolymer of acrylic acid (sodium salt), divinylbenzene, and a cycloaliphatic compound with more than two vinyl groups [127]. Ivosin RK ointment has been studied for its efficacy for prophylaxis of nickel-induced contact dermatitis in vitro. Nickel-containing earrings were coated with Ivosin RK ointment and then immersed in human sweat or lactic acid. It was found that the amount of Ni^{2+} liberated in medium from the earring reduced significantly after coating with the ointment. 129 mg of Ivosin RK could bind 0.076 mg Ni^{2+} after 1 h. The binding of Ni^{2+} was dependent on the surface area exposed, not on the volume of cream, i.e., applying a thick layer of cream did not enhance binding capacity [127, 128].

18.3.2.3 Nanoparticle-Based Barrier Creams

Calcium Carbonate and Calcium Phosphate Nanoparticle-Based Cream

Nanoparticles provide a large surface area to volume ratio and may decrease the dosage required for topical applications of barrier creams and chelating agents. As a result, nanoparticles may reduce the side effects which result from high levels of exposure to chelating agents. Using nanoparticles in the preparation of a cream may be a more effective strategy to prevent the penetration of metal ions into the skin. Considering the advantage of nanoparticles, Vemula et al. have prepared a glycerine-based emollient containing calcium carbonate ($CaCO_3$) or calcium phosphate ($CaPO_4$) nanoparticles with a size range of 70–500 nm to scavenge nickel ions in solution and on the skin [129]. Both compounds are generally recognized as safe (GRAS) agents by the US FDA. It has been reported that particles below 20 nm in size can penetrate the skin, and these particles were specifically designed to be larger than 50 nm to avoid skin penetration. These nanoparticles sequester nickel metal ions through either cation exchange or absorption. $CaPO_4$ nanoparticles showed an 11-fold decrease in the amount of particles required to scavenge 5% $NiSO_4$ in 30 ml of solution as compared to EDTA by mass. 5.56 g of EDTA was required to complete chelation of Ni^{2+} ions from 30 ml of 5% $NiSO_4$, while $CaPO_4$ nanoparticles needed only 0.5 g to capture the same amount. Thus, nanoparticles can maximize the extent of sequestration of metal ions and minimize the dosage. The efficiency of nanoparticles to scavenge nickel has been evaluated using full-thickness pig skin (in vitro) and nickel-sensitized C3H/HeJ female mice (in vivo). Nanoparticles (20%, w/v) in glycerine cream effectively prevented the penetration of nickel quantitively (ex vivo). Moreover, $CaCO_3$ and $CaPO_4$ nanoparticles demonstrated the ability to capture both cobalt and nickel, while nickel scavenging was 40% more effective than cobalt. Among $CaCO_3$ and $CaPO_4$, $CaCO_3$ nanoparticles showed 10% higher capturing of cobalt than $CaPO_4$. This data suggests that sequestration of metal ions is based on the cation exchange property of nanoparticles.

18.4 Ongoing Developments

Inspired by these approaches, a Paris-/Boston-based start-up, Skintifique, has recently developed a new-generation metal capture technology, where several types of agents act synergistically to efficiently capture nickel and other metal ions under favorable conditions to generate safe topical products. Data obtained in several countries from real-life users of the first products derived from this technology, as well as a pilot clinical trial ongoing with nickel allergic patients affected with dyshidrosis (manuscript in preparation), suggest the value of this new-generation technology in both prevention and treatment of metal allergy-associated dermatoses.

18.5 Conclusion

Although metals are required for life, overaccumulation of these elements can lead to harmful side effects, from organ damage to allergic reactions. A range of systemic and topical strategies have been developed to prevent and reduce toxic exposure to metal ions. The majority of systemic strategies are based on small molecular (low-molecular-weight) chelators which promote elimination of metal ions. Alternatively, topical strategies focus on reducing exposure. A wide range of small molecular chelator-based topical barrier creams have been developed which have not shown adequate efficacy in preventing metal exposure, primarily due to the skin penetration ability of small molecular chelating agents themselves. In contrast, metal-capturing nanoparticle-based barrier creams have reduced metal exposure and, in turn, prevented metal-induced contact dermatitis, as the $CaCO_3$ nanoparticle-based barrier cream has demonstrated. In the future, patients may benefit from effective barrier creams with these or other metal-capturing agents combined with therapeutic agents.

Disclosure J.M.K., P.K.V, and E.B. hold equity in Skintifique, a company that has developed a proprietary nickel chelation technology and is commercializing products derived from this technology. E.B. is also an employee of Skintifique. J.M.K. and P.K.V. may benefit financially from Skintifique commercial sales of these products if the corresponding IP is licensed or optioned. The interests of J.M.K. and P.K.V. were reviewed and are subjected to a management plan overseen by their institutions in accordance with their conflict of interest policies.

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Part IV

Hypersensitivity to Metallic Implants

19 Hypersensitivity to Hip and Knee Implants

Lauren N. Ko and Peter C. Schalock

Abbreviations

AJL	Aseptic joint loosening
ALTR	Adverse local tissue reactions
ALVAL	Aseptic lymphocyte-dominated vasculitis-associated lesion
CoCrMo	Cobalt-chromium-molybdenum
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
LTT	Lymphocyte transformation testing
mLST	Modified lymphocyte stimulation test
MoM	Metal-on-metal
MoP	Metal-on-plastic
PTFE	Polytetrafluoroethylene
THA	Total hip arthroplasty
TJR	Total joint replacements
TKA	Total knee arthroplasty
THR	Total hip replacement

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19.1 Introduction

Disease of the knee and hip secondary to wear and tear has a long history in humankind. The advent of total joint replacements (TJR) has greatly increased the longevity, productivity, and quality of life for patients with osteoarthritis, rheumatoid arthritis, osteonecrosis, and other pathological conditions. The first joint arthroplasty was performed in London in 1822 by Anthony White. Subsequently, the first prosthetic knee implant insertion was carried out in 1890, and the first artificial hip the following year. Since that time, there have been innumerable advances made in the composition and surgical implantation technique of artificial prosthetics [1, 2].

TJR of the hip and knee rank among two of the most common surgical procedures in the United States and Europe. For innumerable patients, these operations relieve pain and restore function, vastly improving quality of life. The annual number of knee replacements was ~600,000 in 2009, and this number is expected to grow by more than seven times by 2030 [3]. In the United States alone, the number of total hip replacements annually is ~300,000 [3].

While allergic reactions to implanted metallic devices likely are very uncommon, they do exist and may be relevant to both pre- and post-implant morbidity. Unfortunately, the prevalence, pathophysiology, and proper evaluation required for possible allergic responses to hip and knee

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replacements prior to or subsequent to implantation are currently unclear and fall under the realm of expert opinion rather than evidence-based fact. As an individualized patient-based approach is therefore recommended, we attempt to review the science and draw logical conclusions for the management of patients with TJR.

19.2 Implant Composition

19.2.1 Hip Implants

Hip implants have gone through several stages of development. In the 1960s, first-generation implants were metal-on-metal (MoM) and comprised mainly of alloys of cobalt-chromium. These models had high rates of metal release, as was demonstrated by elevated levels of cobalt, chromium, and nickel found in various areas of the body such as the blood, hair, and urine [4–8], as well as increased rates of metal sensitization. Partially as a response to this, metal-on-plastic (MoP) implants were developed [5], and their use supplanted first-generation MoM devices.

MoP prostheses are composed of metal structural components with polyethylene or cross-linked polyethylene lining. This implant subtype was postulated to induce less metal sensitization because it released large polyethylene wear particles which prevented the formation of allergenic polymer protein complexes [1, 6–8]. Most recently, MoP prostheses have evolved to include highly cross-linked polyethylene, which has proven to produce fewer wear particles than standard polyethylene [9].

In the 1980s, second-generation MoM implants, which were largely made from cobalt alloys, were developed. Shortly thereafter, the improved third-generation MoM implants were introduced. These were uncemented versions of second-generation implants. The third-generation MoM devices were designed to endure high fracture toughness, a mechanical property that measures the resistance to propagation of a crack at the implant surface, as well as to decrease the risk of postoperative instability [6, 10]. The newer MoM models, which were particularly attractive for young active individuals, had a larger head-to-neck ratio, which decreased the risk of impingement and wear, thereby preventing future operations. These implants were made of a variety of metallic elements, the most common being stainless steel, cobalt-chromium-molybdenum (CoCrMo) alloys, nickel, titanium, Vitallium, and vanadium [11]. CoCrMo has been most commonly used for total joint arthroplasty given its comparatively low percentage of nickel [11]. Today, MoM devices are rarely used due to increased rates of patient complications and product recalls [12].

19.2.2 Knee Implants

Knee implants were developed after hip prostheses and differ slightly in their composition and evolution. These implants also consist of metal and plastic: titanium and cobalt-chromium alloys comprise the major metallic components and polyethylene, the plastic components. Knee prostheses can be further stratified by their design type, which includes posterior-stabilized, cruciate-retaining, and bicruciate-retaining.

19.2.3 Bone Cement

Both knee and hip implants are often secured with bone cement. Multiple components of the cement may induce and elicit type IV allergy. Benzoyl peroxide (activator), methyl methacrylate (adhesive), gentamicin (antibacterial agent), and hydroquinone (stabilization agent) have all been reported as potential causes of type IV allergic reactions [13, 14].

19.3 Range and Presentation of Allergic Reactions to Metal

Metal allergy to implants has been described since the 1970s. Metal allergy varies in its presentation and includes localized (Fig. 19.1) and systemic dermatitis [13, 15, 16]. Cutaneous

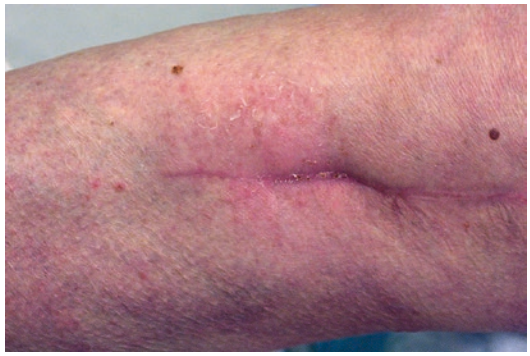

Fig. 19.1 A patient with peri-implant dermatitis following total hip arthroplasty

reactions typically arise within weeks to months of the implantation operation and have been characterized as pruritic, erythematous, edematous, painful, and/or eczematous [14, 17–24]. Hair loss has also been reported as a manifestation of metal hypersensitivity following implantation [25]. Other diagnoses such as infection must always be ruled out prior to suspecting an allergic reaction to metal.

Adverse local tissue reactions (ALTR) around the implanted device are well described in the literature and may manifest as periprosthetic pain, swelling, or even implant failure [14, 18, 20]. The most common non-cutaneous phenomena include aseptic joint loosening (AJL), periprosthetic pseudotumor formation, and aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) [26, 27].

ALVAL and pseudotumors are inflammatory reactions seen most commonly in MoM total hip replacement (THR). ALVAL is considered a type IV delayed hypersensitivity reaction to metal particles released from the device and may occur in areas of low metallic debris [24]. The infiltrate is primarily lymphocytic and may occur independently of or directly preceding pseudotumor development [28]. Pseudotumors, which are neither infectious nor neoplastic [29], show macrophage-induced cytotoxicity to the metallic particles which have been released from the device. Pseudotumors are reported more commonly in women under age 40 [30–33]. Serum metal ion levels are often increased, but this elevation is not predictive of ALTR [34]. An uncommon subtype is a mixed infiltrate, both granulomatous and lymphocytic, surrounding the implant [27].

In metal-on-plastic (MoP) implants, aseptic loosening is an ALTR that may occur due to polypropylene wear particles. These plastic particles lead to a foreign body reaction in the adjacent bone and subsequent inflammation and separation of the prosthesis from the bone [35]. In this situation, periprosthetic necrobiosis and an increased histological lymphocyte count may be seen but is not a specific finding of metal hypersensitivity [36]. Metal debris surrounding the prosthesis are much less common in MoP TJR systems, and it is hypothesized the risk for the development or induction of metal hypersensitivity is lower when compared to MoM TJRs.

19.4 Pathophysiology of Implant Hypersensitivity

19.4.1 Metal Components

The pathophysiology of metal allergy is similar for knee and hip prostheses. Both innate and cell-mediated immune responses play a role in the morbidity associated with reactions following joint replacement.

In orthopedic implants, the surfaces of metallic components interact with the surrounding biologic environment. Osteoclast precursor cells can differentiate on stainless steel, titanium, and aluminum [37]. Matured osteoclasts can corrode metal and release free metal ions in the space around the prosthesis as well as lead to bone resorption and loosening immediately adjacent to the device. These metal ions attach to endogenous proteins, generate an immune response, and recruit pro-inflammatory cytokines [38]. CCR4, a chemokine receptor reported to induce allergic cutaneous reactions, is one such example and recruits helper T cells [37–39]. Given these immunologic phenomena, it is unsurprising that periprosthetic tissue examined after implant failure exhibits significant T- and B-lymphocyte proliferation [38, 40, 41].

Besides the role of cell-mediated immunity, there is a growing literature base describing the

role of the innate immune response in metal allergy. Recent studies suggest that implant debris recruits macrophages and osteoclasts to periprosthetic regions. One mechanism suggests that these cells trigger the NF-κb ligand (RANKL) signaling cascade, leading to bone resorption and possibly contributing to implant destabilization [42]. Still other studies implicate the NALP3 inflammasome within macrophages as a critical mediator of osteolysis [15].

19.4.2 Plastic Components

Plastic polypropylene or ultrahigh molecular weight polyethylene components are used in both knee prostheses and MoP hip prostheses. The pathophysiology of immune reactions to MoM and MoP differs, possibly explaining their varying clinical outcomes. The chief difference is that MoP implants produce a higher volume of plastic wear particles and much lower volume of metal debris, whereas MoM implants generate a larger number of metal particles [43–46]. Further, unlike in MoM implants, a cell-mediated immunopathologic response to ultrahigh molecular weight polyethylene does not seem to lead to implant destabilization and loosening. Nevertheless, pseudotumors, a term describing the development of a nonneoplastic granulomatous soft-tissue mass in the periprosthetic region, are a complication associated with both MoM and much less frequently MoP arthroplasties [47–57]. Unlike the pseudotumors from MoM prostheses, which have a predominantly lymphocytic infiltrate, MoP pseudotumors are predominantly macrophage collections [33, 47, 53, 56, 58]. These pseudotumors, although nonneoplastic, still cause significant damage—a recent case report demonstrated that polyethylene and metal wear particles caused pseudotumor formation that subsequently invaded the patient's vaginal tissue [9]. The pathophysiology of MoM and MoP prostheses indeed differs, and there is no overwhelming evidence that favors one implant over the other. A 2015 study comparing MoP and MoM implants examined the metal levels and chromosomal damage incurred by both and was unable to conclude a statistically significant difference in outcomes between the two subtypes [59].

19.4.3 Bone Cement

Numerous studies have reported hypersensitivity reactions to bone cement agents, which are employed to stabilize implants [60, 61]. Bircher et al. found that patients with failed arthroplasties who patch tested positive to benzoyl peroxide experienced complete resolution of symptoms when their implant was replaced with a bone cement-free implant [61]. Another study found that, among patients with failed arthroplasty, 32% were allergic to one or more components in bone cement [60]. Components, such as *n*,*n*-dimethyl-*p*-toluidine, methyl methacrylate, hydroquinone, benzoyl peroxide, and added antibiotics such as gentamicin or tobramycin, all are potential causative agents within bone cement. Thus, allergy to bone cement components is an important consideration when evaluating a symptomatic implant.

19.5 Metal Allergy to Hip Implants

19.5.1 Early MoM Implants (1st and 2nd Generation)

In a recent review, Cousen and Gawkrodger found that first-generation MoM implants were associated with metal sensitization, and the authors subsequently reported an association but not causation between metal allergy and implant failure [62]. At odds with the above study is a reserve of literature which indicates an unclear relationship between metal allergy and first-generation hip implant complications. Brown et al. examined patients with aseptic loose MoM McKee-Farrar replacements and found that none of this patient subset had metal allergy. In this study, subsequent biopsy of the surrounding tissues in 17 patients undergoing revisional surgery did not show any histologic evidence of allergic reaction to metal [63].

19.5.2 Third-Generation MoM Implants

Regarding third-generation MoM joint prostheses, there is still controversy concerning the role of metal hypersensitivity in adverse postsurgical phenomena. There are many studies suggesting a correlation between metal allergy and postimplantation morbidity. In a study reviewing hip arthroplasty, the rate of sensitivity to nickel, chromium, or cobalt was 25% in patients with well-functioning implants, whereas patients with failed or failing hip prostheses had a rate of 60%, almost six times that of the general population [64]. Another study found that patients with early osteolytic changes in their periprosthetic region had a higher rate of positivity for cobalt patch testing compared to controls [65]. Similar studies with smaller sample sizes also support this association [3, 66, 67]. Others have found that in patients undergoing implant revision surgery due to joint failure, there is a significantly higher rate of metal allergy [67, 68].

Given this association between metal allergy and joint failure, researchers have sought to define the relationship by examining histopathology and biopsies of periprosthetic tissue. There are case reports that link metal allergy to wear particles and implant failure [47, 69–74]. Korovessis et al. found extensive lymphocytic and plasma-cell infiltrates surrounding the metal debris in the periprosthetic tissues of 11 patients who had undergone revision arthroplasty [75], strongly suggesting the association between metal allergy, osteolysis, and subsequent aseptic loosening in MoM articulations. Cancilleri et al. similarly concluded that hypersensitivity likely plays a small role in joint loosening [76]. Other studies also reference the association between these implants with pseudotumors and ALVAL to implicate causality [23, 47, 48, 51, 77]. Specifically, the perivascular T-cell-dominant lymphocytic infiltrate found in many patients with failed MoM implants suggests that there is type IV hypersensitivity involved.

Despite the trends toward causation in the literature, other evidence suggests only a feeble association between metal allergy and implant failure. A large case-control study with 356 cases and 712 controls found that for patients with metal allergies determined preoperatively, the risk of surgical hip replacement revision was not higher compared to those without metal allergy [78]. Waterman and Schrik patch tested patients both pre- and postoperatively and found no evidence to suggest joint loosening based on metal allergy [79]. Granchi et al. similarly found that patch testing was unable to differentiate between stable and unstable hip implants and that the equivalent implant lifespan was not correlated to patch test results [80]. For a succinct, nonexhaustive summary of other such studies, refer to Tables 19.1 and 19.2. Altogether, though an association between metal hypersensitivity and prosthetic hip joint failure has been widely noted in the literature, the strength of this association as well as the existence of causality remains uncertain.

19.6 Metal Allergy to Knee Implants

Metal allergy leading to adverse effects following total knee arthroplasty (TKA) is rarer compared to reported cases of such events with hip prostheses. While no exact prevalence has been noted, Innocenti et al. found that approximately 17% of patients in a small study developed allergic reactions to metal following TKA [95]. Complications following TKA, however, are much more frequently attributed to instability, component loosening, malrotation, referred pain, or chronic regional pain syndrome, all of which must be excluded prior to a diagnosis of metal hypersensitivity [96].

Predictably, there remains no consensus as to the relationship between preexisting metal allergy, allergic reactions, and knee implant complications. Similar to literature on metal allergy in total hip replacement, studies show higher rates of sensitization in patients with unstable knee implants compared to controls. In a prospective study of 94 patients, there was a 20% rate of sensitization to cobalt-based alloys in patients without TKA, compared with a rate of

Table 19.1 Summary of studies suggesting a relationship between metal allergy and implant complications

Study authors	Study type	Joint (resurfacing type)	Summarized results
Hallab et al. [81]	Retrospective	Hip (MoM)	While few (6/22) controls were LTT positive, 8/17 with THA were LTT positive; moreover, 5/7 patients with loose THA were LTT positive
Cancilleri et al. [80]	Prospective	Hip	1/12 patients with aseptic loosening of the joint were patch positive, 2/41 tested preop patch positive; hypersensitivity does play small role in joint loosening
Atanaskova et al. [82]	Retrospective	Both (MoM, MoP)	31 with history of hypersensitivity preop, 21 patch positive, no patients with "allergen-free" implants had complications; 41 suspected of hypersensitivity w/TJA, 10 patch tested positive, 6/10 had resolution of symptoms with allergen-free implant; authors recommend patch testing in those with history of metal sensitivity
Niki et al. [83]	Prospective	Knee	24/92 TKA were mLST positive preop, 5/24 patients who developed postoperative eczema were patch test positive and the rest were not; surgeons should undertake routine preoperative screening for metal allergy
Eben et al. [84]	Retrospective	Both	In cemented TJA, 22/66 symptomatic patients were patch positive; among asymptomatic patients, 3/26 were patch positive
Krecisz et al. [85]	Retrospective	Both	Of 14 patients with poor implant tolerance, 8 were patch positive (7 to nickel, 6 to chromium); 3/14 underwent revision surgery and improved
Evans et al. [86]	Retrospective	Hip	9/14 with loose joints were found to be patch test positive, 0/24 with stable joints were patch positive
Elves et al. [7]	Retrospective	Both	15/23 with failed TJA were patch positive, 4/27 with stable joints were patch positive, 8/13 with cutaneous reaction were patch positive
Park et al. [69]	Retrospective	Hip (MoM)	8/9 with found osteolysis were patch positive to co, 2/9 without osteolysis were patch positive
Zeng et al. [87]	Prospective	Both	49/56 TKA/THA patients patch tested positively preop; a relationship between postsurgery pain and metal allergy may exist in both THA and TKA patients; larger samples and longer follow-up time are needed
Munro-Ashman et al. [18]	Prospective	Hip (MoM)	16/35 with unsatisfactory MoM prostheses were patch positive to metals (13 to cobalt, 4 to nickel, and 2 to chromate); 2/35 patients had cutaneous lesions; patients needing metal prosthesis should be asked about history of metal sensitivity and should be patch tested with metals prior to surgery
Antony et al. [71]	Prospective	Hip	3/5 with loosened hip prostheses developed metal hypersensitivity reactions; results suggest a relationship between loosening and metal sensitivity in patients with MoM implants
Korovessis et al. [79]	Retrospective	Hip (MoM)	Histologic examination of all 11 patients (out of 217 patients) who underwent revision surgery for aseptic loosening or technical failure showed metallosis and extensive lymphocytic/plasma-cell infiltration; periprosthetic osteolysis and aseptic loosening in MoM hip prostheses is associated with hypersensitivity to metallic debris; prospective, randomized long-term studies are needed to confirm the correlation

MoM metal-on-metal, *MoP* metal-on-plastic, *THA* total hip arthroplasty, *LTT* lymphocyte transformation testing, *mLST* modified lymphocyte stimulation test

Table 19.2 Summary of studies showing unclear association between metal allergy and implant complications

Study authors	Study type	Joint (resurfacing type)	Summarized results
Brown et al. [67]	Retrospective	Hip (MoM)	0/20 patients with loose McKee-Farrar hip replacements was patch test positive to nickel, cobalt, or chromium
Granchi et al. [88]	Prospective	Hip (MoM,MoP)	Patch testing of cobalt, nickel, chromium did not differentiate between stable (27/53 were patch test positive) and loosened implants (40/104 were patch test positive); lifespan of patients with positive patch testing was shorter
Waterman et al. [89]	Prospective	Hip (MoP)	13/85 patch test positive preop., 25/85 patch test positive postop., 0/10 patients with loose THA was patch test positive; no evidence to suggest loosening and metal hypersensitivity are related
Carlsson et al. [90]	Prospective	Hip (MoP)	13/134 MoP patients patch test positively postop.; unsure if hypersensitivity caused by THA, but, in patients with history of allergy, proceed with caution
Nater et al. [91]	Prospective	Hip (MoP)	0/66 patch positive preop., 2/66 patch test positive to nickel, 2/66 patch positive to cobalt chloride postop.; 0/66 had clinical sequelae, therefore no need to test preoperatively for metal allergy
Rooker et al. [92]	Prospective	Hip (MoP)	6/69 patch positive preop., only 1/54 patch positive postop.; no clinical sequelae for any patients, no need to screen metal allergy for MoP patients
Verma et al. [20]	Retrospective	Knee	7/15 TKA patients that had cutaneous side effects postoperatively had positive patch tests
Deutman et al. [70]	Prospective	Hip (MoM)	14/212 patch positive for nickel/chromium/cobalt preop., 2/15 patients with metal hypersensitivity reaction postoperatively were found to be patch positive, 4/66 patients developed sensitivity to nickel or cobalt postoperatively
Reed et al. [93]	Retrospective	Both	~25% with history of preoperative hypersensitivity patch test positive, 0% referred for patch testing postoperatively were patch positive
Webley et al. [94]	Retrospective	Knee	16/50 were patch test positive postoperatively, 17/50 experienced either loosening or a persistent sterile discharge from the knee; no correlation was found between these complications and patch testing positivity; authors conclude that metal sensitivity is probably not a primary factor in the pathogenesis of complications, particularly loosening
Milavec-Puretic et al. [72]	Retrospective	Hip (MoM)	9/40 patients with failed hip implants were patch test positive postop.; resurgence of metal allergy with the increased use of surface MoM hip replacements; prospective studies required to decide if metal allergy leads to loosening

MoM metal-on-metal, *MoP* metal-on-plastic, *THA* total hip arthroplasty, *LTT* lymphocyte transformation testing, *mLST* modified lymphocyte stimulation test

48.1% in those with a stable knee implant and 59.6% in an unstable implant [89]. This particular study also found that implant failure was 400% more likely in patients with a preexisting medical history of metal allergy prior to undergoing knee replacement. Another study found an association between preoperative lymphocyte stimulation testing for chromium and the incidence of metal-related eczema following implantation [88]. In light of this association, Zeng et al. conducted a prospective study in which they preoperatively patch tested patients undergoing total hip and knee arthroplasties. They subsequently reviewed the patch tests for those with persistent postsurgical pain and concluded that a relationship between metal allergy and their postoperative symptoms existed [97]. Patient self-report of metal allergy is associated with decreased functional outcomes and reduced mental health scores following surgery [98].

On the other hand, skepticism also exists concerning the relationship between metal hypersensitivity and knee joint failure. In 2016, Bravo et al. showed that patients who patch tested positively did not have a higher TKA complication, reoperation, or revision rate compared to patients with negative patch testing and controls [99]. This same study found no difference in postoperative pain between patients with negative and positive patch tests, which is at odds with Zeng et al.'s study mentioned above [97]. Other small studies of TKA patients have found no association between positive patch tests and loosening of prostheses [83]. Middleton and Toms concluded from their recent review that, although a relationship certainly exists, there is no evidence that implant failure is directly due to allergy [87].

Allergic reactions to metal components in both knee and hip prostheses are rare, and other diagnoses must be considered prior to suspecting allergy. However, these cutaneous and systemic reactions remain an important diagnosis for clinicians to consider, recognize, and manage. Though the literature is still controversial, the mechanisms proposed and associations found suggest that metal allergy may play a role, albeit small, in prosthetic knee and hip joint failure.

19.7 Prevention and Management of Allergic Reactions to Metal

19.7.1 Preimplantation

In preventing adverse effects following knee or hip prosthesis surgery, it is essential to identify which patients would benefit from presurgical testing. Approaches to preoperative evaluation vary widely, from the expert opinion of orthopedic surgeons in Britain who suggest that metal allergy need not be considered prior to surgery [100] to those in Germany, where titanium implants are suggested for empiric use in those with high suspicion of metal allergy [101]. Testing prior to surgery is uncommon in Denmark and Sweden [94]. In the United States, the recommendations of the American Contact Dermatitis Society suggest that only patients with significant history of metal hypersensitivity reactions should be considered for testing prior to surgery [102].

In emergent life- or limb-threatening situations, necessary interventions take precedence over evaluation for metal allergy. In these situations, surgeons should proceed with the best possible and subjectively least allergenic device. In general, titanium alloys may be preferable for empiric use if there is a question of metal allergy.

The role of preoperative testing is more complex in elective surgeries. Asymptomatic patients or those not specifically concerned about metal allergy do not need routine screening. In those with a self-reported history of metal reactions, more thought is necessary. Unfortunately, self-reported history is not a reliable predictor of metal allergy prior to implantation [103]: for example, in 369 women screened for preexisting metal allergy prior to patch testing with self-reported history [103], screening alone showed positive predictive values of only ~60% for nickel allergy. Middleton and Toms found no relationship between allergy and implant failure, though they did find an association between self-reported metal allergy and decreased functional outcomes after TKA and decreased mental health scores after total hip arthroplasty [87].

Table 19.3 Suggested patch test allergens by type

Metals	Bone cement components	Antibiotics	Other
Aluminum	Methyl methacrylate monomer	Gentamicin	Epoxy resin, bisphenol A
Chromium	*n*-Butyl methacrylate	Tobramycin	
Cobalt	Polymethylmethacrylate polymer	Vancomycin	
Iron	Benzoyl peroxide		
Manganese	*N*,*N*,-Dimethyl-*p*-toluidine		
Molybdenum	Hydroquinone		
Nickel	Barium sulfate		
Niobium	Zirconium chloride		
Phosphorus	Zirconium oxide		
Silicon	Polyethylene		
Tantalum			
Titanium			
Tungsten			
Vanadium			
Zirconium			

While it cannot be definitively proven that hypersensitivity to implanted metal devices causes morbidity and prosthesis failure in some patients, it remains prudent to consider preoperative patch testing in individuals who voice history of or concern for metal allergy. At this time, there is no conclusive evidence supporting routine preoperative patch test screening, and it should not be recommended or performed.

19.7.2 Postimplantation

In the postimplantation setting, routine metal allergy evaluation is unnecessary for asymptomatic patients [104]. For those with symptomatic or failed implants, infection and other nonallergic causes of adverse effects should first be considered and ruled out. For those patients who exhibit cutaneous or systemic reactions after implantation in whom other diagnoses have been eliminated, patch testing is reasonable to consider. Experts have suggested various prosthetic-specific series they find useful when screening for allergy [91, 105, 106]. A detailed review of recommended allergens and trays to test based on implant type was published by an international group of dermatologists interested in implant-related metal allergy [91]. In general, testing series should extend beyond just metals and include other potential implant-related allergens, such as bone cement components. A suggested, but by no means comprehensive, list of potential allergens for patch testing prior to orthopedic implant is provided in Table 19.3. Further research is needed to determine the ideal testing series based on patient and procedure.

19.7.3 Management

Management following a positive patch test is controversial, since a positive patch test does not necessarily indicate symptomatic allergic reaction. For asymptomatic patients with a positive patch test, there is no further intervention needed. However, in symptomatic patients, it is necessary to consider whether removal of the implant is feasible, worthwhile, and if it can be done without causing major complications. A discussion between patient and surgeon on the risks and benefits of intervention is merited. Previous studies have suggested potential benefit from replacing the implant with a nonallergenic alloy [107]. If implant removal is not a viable option, a 21-day course of systemic corticosteroids may be beneficial [108, 109]. Although there is no evidence-based management algorithm in place,

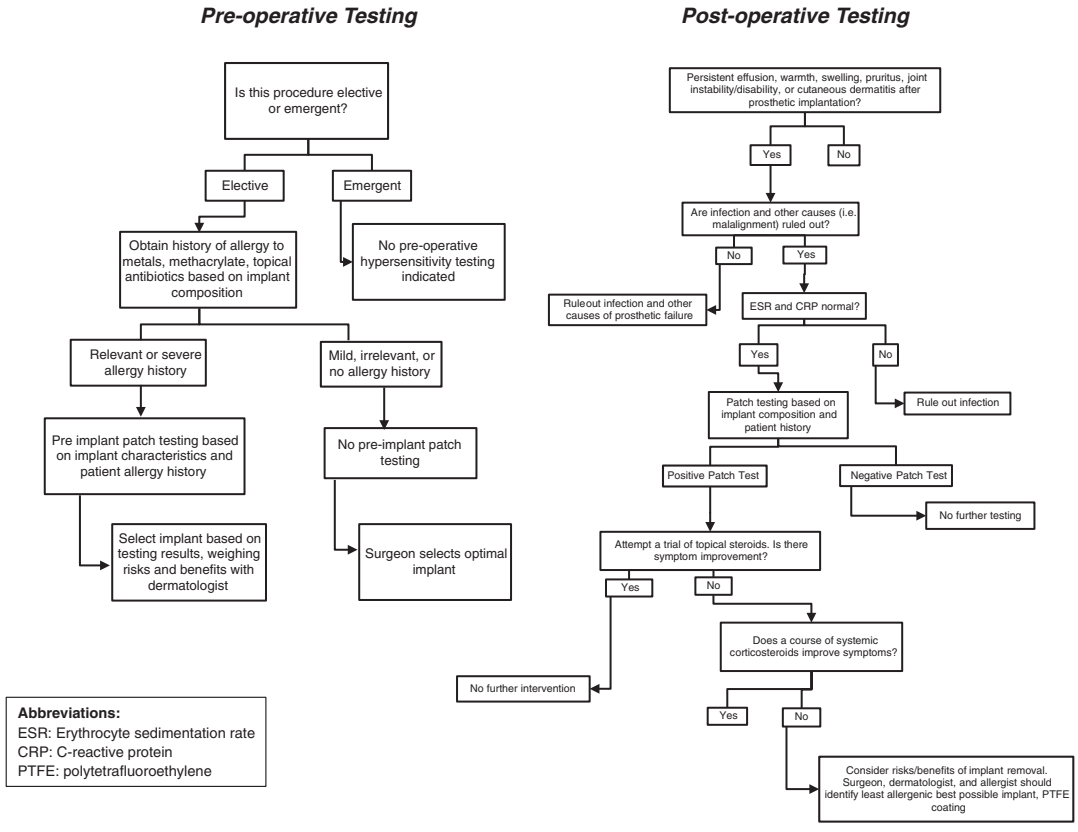

Fig. 19.2 Preoperative and postoperative testing algorithm for assessment of metal allergy (Reproduced with permission from [110])

Fig. 19.2 is a possible guide to approaching testing and management of the total joint replacement patient in both the pre- and postoperative setting.

19.8 Conclusion

As predicted by the Healthcare Cost and Utilization Project, the use of metallic knee and hip implants will continue to increase over time given our aging society. Though the literature appears to document a relationship between metal allergy and implant complications, the strength of this association and the existence of causality is still hotly contested. Also nebulous is the ideal prevention and management of such adverse effects. Prospective randomized controlled trials are merited to further clarify the complex relationship between prosthetic joint implants, metal allergy, and adverse outcomes.

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Hypersensitivity to Cardiovascular Implants: Stents

20

Cecilia Svedman and Magnus Bruze

20.1 Introduction

In medicine, the temporary or permanent use of foreign material in the body has become increasingly common, raising the question of whether an unwanted side effect of implants may be a hypersensitivity reaction. With regard to cardiovascular stents, there are few studies addressing the possibility of hypersensitivity to stent material, mostly small and all, to our knowledge, retrospective studies and case reports. Thus, in clinical practice, it is difficult to evaluate a patient with a stent when the question of metal allergy arises.

With an increasingly ageing population where the problem of coronary artery disease is not diminishing, there is constant innovation in percutaneous coronary interventions (PCI) and stenting. This makes even more difficult giving general statements on if and how patients should be investigated. In order to make possible giving the patient/referring clinician information regarding whether an investigation should be performed, how it should best be performed, or a correct explanation as to why it is not advised to investigate a possible contact allergy, some knowledge on the actual PCI procedure and stents is of value.

We have therefore aimed to provide a deeper understanding of PCI, stenting and the general development of stents. It must be remembered that major complications with the stent procedure, namely thrombus formation and restenosis, very briefly described below, are largely explained by other factors than hypersensitivity.

20.2 Percutaneous Coronary Interventions and Stents

In 1977, the first percutaneous coronary intervention procedure was reported [1]. With balloon angioplasty alone, there is a risk of artery recoil, restenosis and also immediate occlusion due to dissection, intima flap and thrombus formation. Bare metal stents were introduced to avoid recoil and keep the vessel lumen patent [2, 3]. However, while preventing late lumen narrowing due to vascular remodelling, the bare metal stents also triggered neointimal proliferation, leading to in-stent restenosis [4]. The neointimal hyperplasia was thought to occur as a response to vessel injury and actually led to in-stent restenosis and ischemic events in up to one third of cases in

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1-year follow-up [5]. In order to reduce proliferation, neointimal hyperplasia and local inflammation, stents coated with anti-proliferative or immunosuppressive drugs (drug-eluting stents, DES) were introduced, which have substantially reduced in-stent restenosis [6–8]. The first-generation DES did, however, have an increased risk of stent thrombosis, seemingly due to delayed or insufficient healing [6]. The improvements in subsequent generations of DES now actually make the DES the standard of care in percutaneous coronary intervention [6, 9]. Still, clinical problems exist, including late stent thrombosis, stent malapposition and neoatherosclerosis [10, 11]. The permanent metallic stent as such is still associated with chronic local inflammation and hypersensitivity [6, 12, 13].

Bioresorbable stents (BRS) have now been introduced [6], and several BRS platforms are under development. The BRS have potential advantages such as possible restoration of vascular physiology and improved mechanical flexibility [6]. The bioresorbable materials that have been tried are, for example, polylactic acid, tyrosine polycarbonate, poly(anhydride-ester) salicylic acid and bioresorbable metals, especially magnesium [6, 14, 15].

The evolution of minimally invasive endovascular technology has revolutionized patient care, leading to a reduction in age-related cardiovascular deaths over the last 25–30 years [16]. However, with a growing ageing population and an increasing epidemic of obesity [17], the prevalence of coronary artery disease and the need for new treatment strategies will not decrease.

20.3 Stent Design

The device design can have profound effects on functionality: the shape, thickness, coating, scaffolding (i.e. the potential to withstand the elastic forces of the artery wall) and stent coverage (i.e. how much of the stent material is in contact with the vessel wall) are of utmost importance [18]. Material selection and imaging are also factors that are of major importance [19]. This means that there is a multitude of different alternatives within each different stent type. For example, with regard to material, the same material can be used in stents with different stent coverage, thus changing performance and also changing the side effect profile. The rapid influx of new devices aiming at satisfying different needs makes it more difficult to get an overview of the possible, albeit presumably more limited, side effects that may occur with stenting, such as possible hypersensitivity reactions.

Basically, stents can be classified according to their mechanism of expansion (self-expanding or balloon expandable), composition (stainless steel, cobalt-base alloy, inert or active coating) and design (coil, mesh structure, ring, covered stents, etc.) [20]. Bare metal stents are made of different metal alloys and can furthermore be coated. Commonly used materials are 316L stainless steel, chromium, nitinol, titanium or cobalt-chromium.

At the surface of a metal, a reaction may occur with the surrounding environment, creating a surface oxide layer which protects the underlying metal from further corrosion. The protective layer depends on the material and the manufacturing process [21]. Handling can also influence corrosion resistance. Most alloys are heat-treated during construction, giving rise to a polycrystalline oxide on the surface.

20.4 Coating

Stent coatings can broadly be classified into three types: biocompatible coatings, drug delivery coatings and polymer-free coatings. Since metallic stents will release ions leading to inflammatory reactions, initial coatings, usually inorganic material, were created to provide the surface of the stent with an ion release barrier as well as promote good compatibility. Biocompatible coatings include inorganic coatings such as gold, silicon carbide, iridium oxide, titanium-nitride-oxide and carbon.

Drug delivery coatings consist of the carrier of the drug, the polymer and the drug itself. Polymer coatings are large molecular compounds connected with covalent chemical bonds; apart from

being biocompatible, these coatings can also carry and locally release therapeutic agents. Polymers can be either hydrophilic or lipophilic; the former polymers have less surface tension and thus higher biocompatibility, while the latter facilitates drug loading and delivery. Thus, a balance must be sought. The therapeutic agent is present to give the vessel area a local anti-inflammatory chemotherapeutic effect. Initially, two different agents were used: paclitaxel and sirolimus, where the former interferes with cell mitosis and the latter blocks protein synthesis, cell cycle progression and migration. Of the two, sirolimus and its analogues have become the most used [22, 23].

The earliest DES had a coating of poly(butyl methacrylate) and ethylene-vinyl acetate or styrene-isobutylene-styrene, and later polymers are poly(butyl methacrylate/hexyl methacrylate/vinyl and acetate/vinylpyrrolidone) or poly(butyl methacrylate) and poly(vinylidene fluoride/hexafluoropropylene) [22]. Due to risk of an inflammatory response, biodegradable polymers have been introduced, where the most common materials are polylactic acid, polyglycolic acid and the copolymer, polylactic-co-glycolic acid [24]. The accumulated acid products from degradation may lead to inflammatory responses in the vessel [22, 24, 25].

20.5 The Effects of Stenting on the Vessel Wall

Vascular stents are more or less embedded in the vessel wall when used. This of course means that the endothelium is damaged or the vessel completely denuded. To repair the damage, a new intima develops, covered with new endothelium. Soon the stent is covered by this new lining and is no longer in contact with the flowing blood. This process can be disturbed at different levels, causing clinical problems or even stent occlusion due to thrombus formation or intimal hyperplasia [26]. The stent, when damaging the endothelium, will expose subendothelial tissues that are thrombogenic. This may lead to activation of the coagulation system and concurrent thrombus formation [26]. Initially, this will occur on irregularities and turbulent zones of the injured area [26]. Platelets adhere to injured sites and release platelet-derived growth factor, attracting vascular smooth muscle cells and stimulating mitogenic activity [26]. The smooth muscle cells will proliferate and migrate through openings in the internal elastic lamina and form a neointima. This process is quicker in animals than in man [26, 27]: in a rat model, the maximum proliferation of the intima was seen after 96 h. However, smooth muscle proliferation continues also after this, probably caused by activation of the media muscle cells themselves, endothelial cells and macrophages [26–29]. The newly formed neointima has increased permeability, facilitating the diffusion of growth factors until the endothelium is re-established.

The endothelium originates from intact endothelium outside the stented vessel segment and from endothelium located on the tissue protruding between the stent struts [30]. The maturation of the endothelium [31] takes weeks and is in part influenced by local flow conditions as, with low flow, the cells will be deformed and have a rougher surface [26, 31]. The time necessary for endothelialization varies depending on stent dimensions; thus, coverage can vary from one to several months [26, 32]. In most animal studies, the neointimal layer plateaus in thickness several months after stenting, with a maximum thickness 2–6 months after stent placement [33, 34]. Later, for unclear reasons, the intima may actually decrease in thickness, which may increase the diameter of the vessel lumen. When studying these segments years after stent implantation, the intima has been found to contain mostly collagen and fibrocytes, resembling scar tissue [26, 35].

The neointima formation may also be excessive, leading to in-stent restenosis and occlusion [26, 36, 37]. Restenosis may present as a localized restenosis, a diffuse in-stent restenosis and, the clinically most difficult to treat, a proliferative restenosis where the stenosis expands beyond the limits of the actual stent material. The explanation as to why this happens is not fully understood and may originate from haemodynamic changes causing neointimal hyperplasia as an

attempt at remodelling [26]. Drug-eluting stents were introduced to prevent iatrogenic excessive neointimal hyperplasia and reduce the risk of restenosis when using bare metal stents [22, 38–42].

20.6 Hypersensitivity Reactions and Stents

Allergic reactions due to endovascular devices in general and stents in particular are not fully understood. An adverse effect or function of the immune system is considered an immunocytotoxic effect [20, 43, 44]. Immunocytotoxic effects include hypersensitivity, chronic inflammation, immunosuppression, immunostimulation and autoimmunity. Hypersensitivity reactions are usually classified into four types (according to Gell and Coombs). Type I is usually associated with complete allergens and IgE related, type II cytotoxic and IgG/IgM mediated, type III immune complex mediated (IgG/IgM immune complex) and type IV cell mediated. Cardiovascular stents have been mainly associated with type IV reactions, and these will be focused upon in this chapter.

20.6.1 Bare Metal Stents

Bare metal stents in themselves provide a risk of excessive neointimal proliferation. There are several reasons for this, the design being one reason but the metal also playing a part [45]. Bare metal stents will release ions, since they are subject to corrosion. Stainless steel, a metal alloy widely used in stents, has been shown to release ions that will induce reactive oxygen species, inflammation and fibroproliferative responses [26]. In order to give rise to a type IV reaction, metal ions then have to be protein-reactive to become immunogenic and evoke the adaptive immune response. It has, however, been shown with regard to nickel and cobalt that metals can also trigger the innate immune system [46, 47]. With regard to metals and the endothelium, we have not found specific studies addressing this. The metal and how it is used, in an alloy or as a plating, will influence metal release [48–50]. Furthermore, the local environment of the metal object will influence release [48], this being perhaps most evident with regard to the oral mucosa and dental alloys, where metal release is influenced by masticatory forces, changes in pH, saliva, temperature and also microorganisms [51]. Thus, the basic stent material and the local environment will influence metal release. Also the coating, as mentioned and as will be further described, will have an impact on metal release.

Is metal release sufficient to elicit sensitization or a localized contact allergic reaction? What symptoms will there be from such a reaction and how can it be objectified? A contact allergic reaction involving the endothelium in a stented area would most probably give rise to an inflammatory reaction, possibly causing secondary excessive neointima formation. The relationship between contact allergy to metals, a stent made of the metal investigated, and in-stent restenosis has been investigated. A possible association between stents and metal allergy has been shown. With regard to stents, investigations have been mainly limited to retrospective studies and show somewhat disparate results. One meta-analysis has been performed by Gong et al. [52]. In this study where nine articles (total number of patients, 1223) [53–61] were scrutinized, it was found that being allergic to stent material was related to a risk of in-stent restenosis (OR = 2.65, 95% CI 1.83–3.82). Of the studies, four concluded that the risk of in-stent restenosis was higher in allergic patients, and five reported no statistical difference in this aspect [52]. As the studies were all retrospective, the stents evaluated in these studies did differ and were not always controlled, and also the definition of in-stent restenosis was not always clearly defined. In the study by Svedman et al., two patient groups and a control (dermatitis patients) were studied [48]. The stented population had been stented with anatomically identical stents, but one subgroup was gold-plated. Gold and nickel were the two major allergens studied, and in an

in vitro analysis, it was shown that the stents did release the metals analysed [48]. A relationship was found between gold stents and contact allergy to gold, and a higher frequency of nickel allergy that did not meet statistical significance was found in the stainless steel (i.e. nickel-containing alloy) stent group. As has previously been found, there was an association between dental gold and contact allergy to gold, but in a multivariate analysis where this was considered, there was still an increased frequency of gold allergy observed in the gold-stented population [62].

A higher concentration of gold in blood was also found [63], indicating the possible continuous release of gold (and thus circulating hapten) from the stent. Furthermore, when analysed, there was found a significant correlation between gold stents, contact allergy to gold and restenosis. This was not found in the nickel group where stents with no plating had been used. The correlation remained after adjusting for various factors that might influence restenosis rate such as diabetes, stent length, etc. [58]. It should be noted that gold-plated stents are no longer used due to their higher restenosis rate (regardless of the cause).

Further and possibly prospective studies are necessary in order to investigate whether metal stents can induce contact allergy or, in those allergic, impact the restenosis rate. It has to be taken into consideration that the use of coating, especially when DES are used, may influence metal release and its sequelae [64–66].

20.6.2 Drug-Eluting Stents (DES)

Despite the promising results associated with the first-generation DES after introduction, several safety issues were raised [67–69]. Lack of biocompatibility leading to persistent inflammation, risk of continued neointimal response and late in-stent restenosis, and delayed/incomplete healing with risk of late stent thrombosis were concerns that were raised. In addition, other issues were identified, including stent malapposition (early or late acquired), the risk of early or late stent fracture, neoatherosclerotic lesion formation and late DES failure, and the permanent metallic caging causing abnormal vasomotion [70]. With the latter, abnormal vasoconstriction responses to acetylcholine at sites distal to the DES were identified, implying abnormal function of the endothelial layer.

The first-generation DES were also investigated due to concern for hypersensitivity reactions. These included rash, dyspnoea, hives, itching and fevers [20, 71]. In total, 262 cases were reported and investigated [71], during a time when more than two million DES stents had been used worldwide. Several causatory variables were discussed, such as medication given peri-procedurally, the drug that the DES was impregnated with and the stent itself, including both the metal components and the polymer coating. Seventeen distinct cases of putative stent allergy were identified. In four of these cases, the patients died of coronary thrombosis, and upon histological examination on autopsy, intra-stent eosinophilic infiltrates and poor intimal healing were found in all four cases [20, 71].

Although rare, these data suggest a spectrum of hypersensitivity response to DES. No specific allergen has been found, however. Bare metal stents have not been demonstrated to cause hypereosinophilic IgE-mediated reactions (71, 72). The polymers of the DES are more likely to be the cause of late persistent hypersensitivity [20, 71], which has also been shown in studies on porcine coronary arteries demonstrating that some biodegradable and non-biodegradable polymers are capable of inducing a marked inflammatory reaction and neointimal thickening [72]. Although newer-generation DES, with more biocompatible polymers, overcame many of the safety issues related to first-generation DES, these concerns were not completely resolved, especially the long-term risk of DES failure secondary to neoatherosclerosis [73, 74]. Of note, the polylactic acid/polyglycolic acid copolymer showed the least amount of fibrocellular proliferation, and its subunits polyglycolic acid (PGA) and polylactic acid (PLA, also known as PLLA) are some of the polymers being utilized in

bioabsorbable products. The side effect profile, including possible hypersensitivity reactions, of the most recently developed stents (i.e. biodegradable platforms) is still under evaluation [73, 75].

20.7 Evaluation for Possible Hypersensitivity Reactions in Patients Who Have Undergone Cardiovascular Stenting

Several diagnostic protocols with regard to implants have been suggested [20, 76–78]. A subset of patients with metal hypersensitivity may develop cutaneous or systemic reactions to implanted metals following implant. At a minimum, patch testing with an extended baseline screening series, metal screening and glue series is necessary.

General recommendations include the following:

1. A careful history must be taken with the aim of elucidating, if possible, what reaction type the patient has.
2. History should be taken regarding contact sensitivity or possible reactions to metals. Note that patients may mistakenly refer to pressure urticaria as a possible contact allergic reaction. The lack of a history of metal item dermatitis does not predict negative metal patch test reactions [79, 80].
3. Reactions to other possible agents either in/on the stent or that have possibly been involved peri/post-operatively have to be investigated. Obtain information on the device, list of biomaterials and possible sterilizing agent.
4. Try also if possible to get information on any other implant(s) the patient may have. With regard to gold, it has been shown that the total systemic load of the hapten may be of importance as to whether there will be symptoms [81–83].
5. Patch test according to exposures (at optimal dose and with two readings) and, if possible, with the material as is or with an extract of material used in the device. Remember that if a material is degradable/reactive, new components may form. Obtain a history of other allergies such as latex allergy (latex prick test, serum IgE level).

Even if an allergy is found and the stent is known to release the hapten, stents cannot be removed. Thus, if the patient has clinical symptoms, a slow tapering of prednisolone has been advocated [80, 83]. If there are prevailing symptoms, the total load of haptens must be considered and whether removal of part of the total load may relieve symptoms [80]. These patients should of course not be subjects for new implants of the same material.

20.8 Patient Recommendations

A common concern when PCI and stenting are recommended is whether patients should be patch tested prior to the procedure. Many of these patients are treated under acute circumstances, and with current knowledge, there is really no reason to advocate patch testing prior to PCI and stenting even if there is a substantial history of reactivity to metals [20].

It should be taken into consideration that stents may release metals very differently and that metal allergy to many of the metals in stents is very common in the population [84, 85]. It is furthermore important that it be shown whether the hapten actually is released from the implant to be used and to quantify this release, if possible. For example, a stainless steel implant may release very little nickel, and with the risk for elicitation being very difficult to foresee in a nickel-allergic individual, a stainless steel stent with better performance may be unnecessarily discarded due to a known positive reaction to nickel, despite the fact that the amount of allergen released may be of no relevance. The threshold of reactivity of the patient then becomes extremely important, and a dilution series should if possible be used for patch testing. Those without a history of dermatitis should not be tested unless considerable concern exists. Even if a metal allergy is found, it may be very difficult to give advice as to how the patient should be treated, and this should be taken

into consideration prior to testing. In order to gain a better understanding of this complex and controversial topic, prospective randomized and controlled studies are required.

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21 Hypersensitivity to Cardiovascular Implants: Cardiac Implantable Electronic Devices and Septal Occluders

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21.1 Introduction

Advances in procedural medicine and availability of numerous biomedical devices in various medical and surgical specialties are improving quality-of-life and life expectancy in many patients. However, for a select group of patients, the issue of hypersensitivity to component(s) of medical devices is a concern. Since the early 1970s, allergic reactions to nickel in patients with metallic mitral valves and orthopedic prostheses have been reported [1–4]. Evaluation of putative hypersensitivity reactions to implantable devices requires a comprehensive understanding of the complex surgical, mechanical, environmental, and biologic factors that can affect the outcome of device implantation. Allergic reactions to endoprostheses are rare and unpredictable processes that are not fully understood. Hypersensitivity reactions can potentially be induced by metallic and non-metallic components of a device. Since the focus of this chapter is on the association of metal allergy and medical devices, review of the metal compositions, corrosion, and interaction with the immune system discussed in earlier chapters is highly recommended.

It is of note that there is an increasing trend of metal allergy in younger generations, at least in the United States. In a recent report of patients patch tested by the North American Contact Dermatitis Group, the frequency of positive patch test reactions to nickel was 10% in individuals older than 65 years of age, 17% between 18 and 65 years, and 25.9% in those younger than 18 years [5]. Although these numbers overrepresent the prevalence of nickel allergy in the general population, they can highlight an increasing trend in frequency of metal allergy. Enforcing regulatory measures on the amount of nickel release from consumer products has lowered prevalence of nickel allergy in Europe, but currently there are no similar regulatory measures in the United States [6–9]. Concern about metal sensitivity associated with implantable medical devices has a growing impact on quality-of-life and healthcare costs. There is an expanding interest in the proper evaluation of individuals with suspected metal allergies prior to receiving an implant or postoperatively in patients with localized or systemic hypersensitivity reactions or, at times, with implant malfunctions.

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21.2 Pacemakers and Implantable Cardioverter Defibrillators

Cardiac arrhythmias are common and important public health concerns. While many patients are managed by medical interventions, a large proportion of them need to be treated via invasive electrophysiology interventions such as ablation therapy and/or cardiac implantable electronic devices (CIED). From the implantation of the first pacemaker in Sweden in 1958, there have been many advances in this field [10]. Device-based antiarrhythmic therapy is a dynamically evolving field of cardiovascular medicine. The main CIED include the pacemaker, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) device. It is estimated that more than one million pacemakers and more than 320,000 implantable cardioverter defibrillators are implanted annually worldwide [11]. About a quarter of pacemaker implantations and a third of ICD implantations are replacements for various indications [11]. Putative hypersensitivity is an extremely rare condition that may lead to device replacement.

21.2.1 General Device Characteristics

In general, these devices are made of two implantable components: generator and lead(s). Generators for the most part are covered with a titanium capsule, and leads are attached to the capsule through the pacemaker's header which is composed of two main components: (a) poly-methyl-methacrylate (also used for bulletproof glass and hard contact lenses) and (b) silicone rubber (polydimethylsiloxane). Some headers are fully Silastic (a flexible inert silicone rubber). The sensing/pacing leads are flexible insulated wires, which are connected to the pulse generator header on one side and carry the impulses to the heart, stimulating the heart through the pacing electrodes. Leads also carry information from the heart back to the pulse generator, which the physician accesses via a special programmer. The conductor wires consist of MP35N (an alloy of Ni, Co, Cr, and Mo) or MP35N, with a silver core for high-current applications (mainly defibrillation). The pacing electrodes are commonly made of platinum alloyed with 10–20% iridium. ICD leads also have similar pacing electrodes at the tip but additionally have one or two defibrillation electrodes (shock coils) for delivering high-energy cardioversion pulses. The majority of shock coils are made of platinum or platinum-iridium, and the remaining are made of tantalum with platinum coating. Leads are most commonly insulated with one of several formulations of polyurethane, silicone rubber, some copolymers of silicone and polyurethane, ethylene tetrafluoroethylene (ETFE) and polytetrafluoroethylene (PTFE), or polychloroparaxylene (parylene). Steroid-eluting electrode tips are available containing about 1.0 mg of dexamethasone with the intent to lower local inflammation, allowing a lower pacing system energy requirement [12–16].

A number of different pacemakers and ICDs are commercially available, and the specifics regarding product materials can be obtained from individual vendors.

21.2.2 Associated Hypersensitivities

Reported cases of allergy and other reactions associated with pacemakers and ICDs are primarily reports of localized pain and/or dermatitis syndromes occurring within 2 days to 24 months after implantation and a few cases of generalized pruritus or dermatitis that resolved after pacemaker removal [17, 18]. Titanium generally has excellent biocompatibility, although it has rarely been associated with cell-mediated hypersensitivity. Diagnosis of titanium allergy based on patch testing is uncommon; perhaps the optimum patch test material for titanium is yet to be established. Allergy to other components such as polychloroparaxylene, epoxy resin, triethylenetetramine, an epoxy hardener, nickel, chromium, cobalt, mercury (with undetermined relevance), polyurethane, polysulfone beige, and silicone adhesive has also been reported [19–26]. Reported cases of putative CIED reactions are listed in Table 21.1. It is important to note in many of these cases reported, information is not complete and presence of a true allergic reaction is difficult to prove.

Table 21.1 Reported cases of metal contact sensitivity associated with cardiac implantable devices

Putative allergen	Reference	Reaction type	Patch test results (as reported)	Other diagnostic methods/ comments on management
Titanium	Peters et al. [44]	Localized dermatitis	Titanium plate++ Nickel sulfate 2.5% +	Patient developed localized dermatitis 2 months after placement of parylene coating; no other information available
	Abdallah et al. [23]	Localized dermatitis/ vesicular	Titanium + Polyurethane +	Pacemaker was replaced with a customized silicon-coated device, but rash recurred; device was removed and patient managed medically
	Viraben et al. [45]	Granulomatous local dermatitis	Negative	Electron probe microanalysis (EDAX) was performed on the skin biopsy, detecting titanium restricted to the granuloma area. Rash cleared with topical steroid
	Yamauchi et al. [46]	Local erythema	Patch test negative to standard trays and pacemaker components	Intracutaneous test with the serum incubated with titanium was positive after 2 days. No information on management available
	Ishii et al. [39]	Localized dermatitis	Titanium metal +	Device was wrapped in a polytetrafluoroethylene (PTFE) sheet, with no recurrence in 3 years
	Freeman [47]	Localized erythema and erosion	Titanium dioxide 50% + Titanium Dioxide 10% +	Pacemaker was replaced by a gold-coated pacemaker with no recurrence
Titanium Nickel Chromium	Dogan et al. [48]	Localized dermatitis over the ICD	Titanium Nickel Chromium	Dermatitis resolved with topical steroids
Chromium Cadmium	Laugier et al. [49]	Localized dermatitis	Cadmium + Chromate +	NA
Nickel Cobalt Chromium	Tilsley and Rotstein [50]	Lichenified plaques on lower extremities	Nickel +++ Cobalt ++ Chromate +	NA
	Landwehr and van Ketel [51]	Pompholyx on both hands	Nickel sulfate 5% in pet. +	
	Moini et al. [52]	Lower extremity dermatitis	Nickel +++ Cobalt +	
Other metals	Brun et al. [25]	Localized dermatitis	Mercury + (undetermined relevance)	
Epoxy	Andersen [22]	Localized desquamation and discoloration	Epoxy resin 1% in pet. + Epoxy resin hardener: ++ (triethylenetetramine 0.5% in pet.)	Pacemaker was replaced by a device in a titanium capsule

Table 21.1 (continued)

Putative allergen	Reference	Reaction type	Patch test results (as reported)	Other diagnostic methods/ comments on management
	Romaguera et al. [53]	Generalized pruritus and erythematous plaques on trunk	Epoxy resin +++	NA
	Skoet et al. [21]	Localized dermatitis	Epoxy resin ++	Dermatitis was controlled with topical steroids
Polychloroparaxylene (parylene)	Iguchi et al. [20]	Localized erythema; dermatitis	Positive patch test to the Polychloroparaxylene (parylene) coating	Parylene coating was stripped off a pacemaker and the device was wrapped in polytetrafluoroethylene (PTFE) sheet with no recurrence in 2 year follow-up
Polyurethane and parylene	Hayes and Loesl [19]	Lead dislodgment and drainage at the implant site	Polychloroparaxylene (parylene) + Polyurethane +	Pacemaker was replaced with specially manufactured device with a Silastic-coated pulse generator and Silastic-insulated leads, and had no other reactions
Polysulfone beige and polyurethane	Dery et al. [24]	Localized dermatitis and pain over the pacemaker	Polysulfone beige and polyurethane 75D, components from the pacemaker lead connector	Pacemaker was replaced with a customized silicon-coated device with no recurrence in 18 months
Thiuram mix	Tujita et al. [42]	NA	Thiuram mix +	NA
Silicon adhesive	Raque and Goldschmidt [26]	Localized dermatitis	Uncured silicone adhesive—neat +++ Uncured silicone adhesive −10% in pet.: negative	Possible irritant reaction on patch test. Pacemaker was not removed. Dermatitis controlled with topical steroid
Unidentified allergen	Verbov [54]	Localized eczema	Negative (titanium not tested)	Granulomatous reaction on histopathology
	Gimenez [55]	Localized eczema	Negative	NA
	Brun and Hunziker [25]	Localized eczema	Negative to metallic titanium and titanium tetrachloride solution	NA
	Buchet et al. [17]	Generalized pruritus and eosinophilia	Not conclusive due to concomitant dermatitis	Dermatitis resolved in 5 days after device removal
	Weiss [18]	Localized erythema	Negative to titanium plate, polyurethane, and European standard tray	Reactions resolved after replacement with a different device
	Tujita et al. [42]	NA	Negative patch test	NA
	Kono et al. [41]	NA	Negative patch test	NA

21.2.3 Evaluation of Patients with Putative Allergic Reactions to CIEDs

A comprehensive approach to patients with cutaneous or systemic reactions following implantation of pacemaker/ICD is essential. Nonallergic reactions are far more common and include infection, reticulated telangiectatic erythema, circumscribed erythema, pressure dermatitis, middermal elastolysis, and radiation dermatitis [27–36]. Infection is a much more common cause of inflammation associated with CIEDs and should be investigated thoroughly before suspecting allergy. A device pocket tissue culture should be performed, although a negative culture does not always rule out the presence of an infection and may only illustrate the limitations in current bacterial isolation techniques. Chua et al. showed that 32% of patients with clinical signs and symptoms of ICD infection had negative tissue and swab cultures, and yet they responded well to treatment with total device and hardware removal and antibiotics [30]. The negative cultures in these cases may have been the result of antibiotics administered prior to clinical presentation for surgical treatment [30, 37]. Routine patch testing is not required prior to implantation of a pacemaker or ICD.

Once other causes are excluded, the management of dermatoses is typically tailored based on clinical findings. Localized dermatitis and mild cases can be treated with topical corticosteroids. In rare cases where allergic reaction is highly suspected, epicutaneous patch testing using relevant allergens customized per device should be performed. If antibiotics are used to irrigate the device pocket prior to insertion, these antibiotics should be added to the patch test panel. In patients with relevant positive reactions to components of a device, replacement of the device with one that is free of the suspected allergen is recommended. An alternative method is wrapping the device generator in a PTFE sheet, which has been successful in preventing recurrence of contact dermatitis [20, 38–43]. Hayes and Loesl reported the case of a patient in whom allergy to polyurethane was documented by patch testing. A specially manufactured device with a Silastic-coated pulse generator and Silastic-insulated leads was substituted and led to resolution of inflammation with no other reactions [19]. Additional reported cases and management options are listed in Table 21.2.

Table 21.2 Evaluation of putative allergic reaction to cardiac implantable devices

(a) Perform a detailed clinical history
(b) Rule out infection; in many cases tissue culture from peri-implant tissue would be most definitive, but this can only be done during the explantation
(c) Consider other diagnosis such as pressure dermatitis and other noninfectious causes such as reticulated telangiectatic erythema
(d) Skin biopsy helps characterize the dermatoses
(e) Consider patch testing only in patients with a significant history of overt contact dermatitis to environmental exposures
(f) Patch testing should be customized toward the components of the implanted device

21.3 Percutaneous Atrial Septal Defect and Patent Foramen Ovale Occluders

A different category of devices reviewed here are devices that are used for closure of holes between the right and left atrium. Two main conditions that cause abnormal flow of blood from the right to left atrium are atrial septal defect (ASD) and patent foramen ovale (PFO). ASD is a congenital heart defect caused by incomplete closure of the atrial septum. It is estimated that each year about

1 in 2000 babies are born with an ASD in the United States [56]. The foramen ovale serves a physiologic purpose in the fetal circulation, helping the flow of oxygenated placental blood from right to left atrium. Soon after birth, this portal will seal; however, in about 25% of healthy individuals, it remains patent. Most patients with PFO are asymptomatic, but several diseases including cryptogenic stroke, transient ischemic attacks (TIA), and migraine headaches with aura have been associated with PFOs. [57–59] A PFO may be the pathway through which thrombotic emboli, air emboli, desaturated blood, and vasoactive substances are shunted and enter the left atrium without traversing the pulmonary circulation. Paradoxical emboli play a role in the development of stroke. That being said, the jury is still out on the clinical benefits of PFO closure for stroke prevention [60].

Percutaneous ASD closure was first performed in 1974 [61]. The first commercially available ASD closure device was developed by Rashkind and Mullins in the early 1980s followed by other devices [62–66]. The first device specifically designed for closure of PFO was designed as a double-umbrella device in 1992 [67]. ASD closure devices can be used to close PFOs as well. The general concept involves approximating the leaflets, closure of the hole between the atria, and subsequent endothelialization of the device. Complete closure of the ASD and PFO is achieved within a few months.

Currently a variety of transcatheter device systems are available for repair of ASDs and PFOs. The US Food and Drug Administration's (FDA) Center for Devices and Radiological Health approved the Amplatzer septal occluder for percutaneous ASD closure and PFO closure [68, 69]. The Amplatzer device is made of two connected circular, self-expanding, nitinol (nickel-titanium alloy) discs that contain thin polyester fabric [69]. Another FDA-approved device is the GORE HELEX septal occluder for percutaneous ASD closure. The implant is made of a circular wire frame made of nitinol and covered with a thin GORE-TEX membrane [70]. Another FDA-approved device to be used only for closure of certain complex ventricular septal defects is the NMT Medical CardioSEAL Septal Occlusion System, which was used off-label for ASD and PFO closure but is currently only used for investigational purposes [71]. The CardioSEAL STARFlex Septal Occlusion System is composed of a metal "double-umbrella" framework made of MP35N alloy and polyester fabrics [71]. The GORE® HELEX® septal occluder is composed of ePTFE patch material supported by a single nitinol wire frame. GORE® CARDIOFORM received FDA preapproval in September 2015 and is made of an ePTFE membrane supported by a platinum-filled nickel-titanium (nitinol) alloy wire frame [72].

The abovementioned devices are all nondegradable with metallic components, but significant advances in this field, including introduction of partially degradable and totally degradable occluders, might change the composition of the applied biomaterials [73].

21.3.1 Hypersensitivity Reactions to ASD and PFO Occluders

Currently, most commonly used occluders contain a metallic frame, and nickel allergy has been identified as the most common cause of surgical device explantation [74].

As mentioned earlier, Amplatzer® and GORE® HELEX® septal occluders have nitinol frames, and the CardioSEAL® occluder is constructed of a cobalt alloy (MP35N) frame.

Nickel elution in vitro was recently studied by Verma et al. in four devices, the Amplatzer septal occluder (ASO; St. Jude Medical Corporation), GORE HELEX septal occluder (HSO; W.L. Gore & Associates), and a new GORE septal occluder (GSO) in clinical trials, which all have a nitinol frame, and stainless steel sternal wires [75]. They observed higher nickel elution with the Amplatzer septal occluder compared to the other devices, which was significantly higher at 72 h and remained higher up to 90 days [75].

In vivo nickel release from the Amplatzer® occluder was studied by Ries et al., who measured serum levels of nickel in 67 patients at 24 h, and 1, 3, and 12 months after occluder

implantation. A statistically significant rise in mean serum levels of nickel was observed from 0.47 ng/ml before implantation to 1.27 ng/ml 24 h after implantation, to a maximum of 1.50 ng/ml 1 month later. Values <2 ng/ml of nickel are considered to be normal [76]. The presence of nickel allergy is listed as a contraindication for implantation of the Amplatzer®.

Burian et al. in another in vivo study of 24 patients following implantation of the Amplatzer® occluder observed increased serum levels of nickel up to fivefold ($p < 0.01$) versus baseline during the first 6 weeks following the procedure. Although serum nickel levels remained within normal limits (serum values ranged from 0.6 ± 0.2 μg/l), they returned to baseline within 4–6 months [77].

Several cases of systemic allergic reactions to PFO occluders without apparent rash but with positive patch tests have been reported to date [78–84]. A few of these patients developed pericardial effusion and tamponade, which resolved with systemic prednisone without removal of the device [81, 85]. In a few of these patients, surgical removal of the device led to recovery with resolution of symptoms [78, 79, 82–84]. In another case, the patient continued to have systemic symptoms even after the removal of the Amplatzer, but he finally recovered following removal of his stainless steel sternal wires, which contained trace amounts of nickel [80]. Considering the thousands of Amplatzer devices implanted over the past decade, the overall incidence of complications associated with metal allergy seems insignificant [86].

On the other hand, no association was found between a positive reaction to nickel on the TRUE test and adverse effects following Amplatzer® implantation in small cohorts [87, 88].

Rigatelli et al. observed a constellation of symptoms in eight out of nine patients who reacted to nickel in the TRUE test, yet decided to proceed with nitinol-based ASD occluders. They referred to these findings as "device syndrome," which consisted of chest discomfort, dyspnea on exertion, asthenia, and mild leukocytosis. The syndrome was treated with prednisone and clopidogrel and in all cases was resolved after 1 week of therapy. In their study ($n = 46$), none of the patients without nickel allergy developed these post-closure symptoms [88].

Despite some conflicting data considering that all these data are from small cohorts and anecdotal reports, it is plausible to obtain at least a clinical history of overt metal allergy as part of the pre-procedural evaluation. Pre-procedural patch testing of patients with suspected metal allergy should be limited to individuals with strong clinical history of metal allergy. Based on available data, presence of nickel allergy is not an absolute contraindication for receiving the occluder devices [88].

Workup for patients with post-procedural complications, including signs of systemic hypersensitivity, eosinophilia, dermatitis, and pericarditis, should include exact details of the procedure including pre- and post-procedural medications and sterilizing methods. Patch testing with metal salts should be considered along with detailed workup to exclude other etiologies.

21.4 General Comments

Long-term prospective data and large-scale cohorts of patients with putative metal allergy to endovascular devices are missing; however, existing data collectively suggests an association between metal allergy and development of localized or systemic hypersensitivity syndromes or neurologic syndromes following implantation of occluder devices in patients who are highly sensitive to metals, most notably to nickel.

The majority of current data regarding putative sensitivity reactions to endovascular devices is based on relatively small cohorts and anecdotal reports. Therefore recommendations listed in Tables 21.2 and 21.3 are mostly based on expert opinion and with limited evidence.

A spectrum of complications, varying from minor localized dermatoses to excessive inflammation, systemic hypersensitivity, and implant failure, are reported in patients with metal allergy. However, as mentioned earlier, only a small portion of individuals with positive patch tests to

Table 21.3 Approach to patients with atrial septal defect or patent foramen ovale occluders

Prior to implantation
(a) A detailed clinical history should be obtained
(b) Only patients with significant history of metal allergy should be considered for patch testing (level III evidence; expert opinion)
(c) Patch testing, if performed, should be conducted with relevant metal salts and device components
(d) Interpretation of positive reactions to metals that are tested as chloride salts such as manganese chlorides in petrolatum should be made with caution due to the high rate of false-positive reactions
(e) Lymphocyte transformation tests should not be performed routinely or as a substitute for patch testing
(f) For individuals with metal allergy, if possible, a device free of the identified allergen or lower elution rate should be considered
(g) Clear discussion with the patient is necessary to inform them that avoiding a potential allergen in the device does not guarantee a desired outcome
Post implantation
(a) Patch testing should only be considered when other causes of failure such as infection, drug eruptions, or other mechanical and surgical etiologies are excluded
(b) In cases of mild cutaneous dermatoses, skin-directed therapies should be optimized to control the symptoms
(c) Decisions regarding surgical explantation are best made though a multidisciplinary approach among treating medical teams

metals will go on to develop complications with their medical devices [89]. Some metal-allergic patients tolerate orthopedic implants containing a metal to which they are allergic, without dermatologic or orthopedic complications [90]. Because methodologies in currently published studies vary widely, special attention is required when interpreting data. Considering the large clinical and economic impact of implanted cardiovascular devices, a multidisciplinary approach is warranted to establish large population-based, multicenter prospective registries and to perform prospective case-control studies, in which methods of sensitivity testing are standardized. In general, patch testing should be tailored toward the specific biomaterials used in a device, in addition to testing with standard screening allergens in select cases.

Most importantly, patients need to be informed that the association between a positive patch test and the outcome of a procedure is still under investigation and, while avoiding a potential allergen in a device should be considered if possible, it does not guarantee a desired outcome.

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Hypersensitivity to Dental Alloys

22

Joris Muris and Cees J. Kleverlaan

22.1 Introduction

Dental elements or teeth may decay mainly due to caries or trauma. A broad variety of dental appliances can be used to restore or replace decayed or missing elements. These appliances may be made of resin-based materials, composites and ceramics, or partially or fully made of alloys. Alloys are by definition composed of more than one metal, and dental alloys usually contain at least four metals and often six or more, making them metallurgically complex [1]. These dental appliances are in use for years to decades. In this section, the different dental appliances are briefly reviewed, and the most important metals used in dentistry are discussed. Most of these metals are reviewed in detail in other chapters of this book. Finally, the path from corrosion to clinically relevant findings is discussed. Specific oral mucosal immune responses are considered in terms of the clinical picture of hypersensitivity to dental alloys.

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22.1.1 A Brief Overview of Dental Applications

An enormous variety of dental applications are available to restore or replace decayed dental elements. Dental applications can be categorized as dental restorations or dental fillings, fixed dental prostheses (FDP), removable dental prostheses (RDP), dental implants and orthodontic appliances.

Dental restorations or *dental fillings* are initially applied in a soft form intraorally (*direct method*). The two main filling materials used nowadays are dental amalgam and composite. The setting of amalgam occurs because of a chemical reaction between mercury (Hg) and a silver-tin-copper (Ag-Sn-Cu) alloy. The resin-based materials are cured due to a polymerization reaction, initiated by blue light in the range of 400–500 nm. The quality, in terms of mechanical properties and 'biocompatibility', of amalgam and composite restorations is to a large extent operator dependent.

Fixed Dental Prostheses (FDPs) or (partial) dental crowns and bridges are applied to teeth that are severely decayed or to replace lost and/or missing teeth. These restorations are fabricated outside the mouth (*indirect method*) and then fixed with cement onto the tooth. These constructions can also be cemented or screwed to endosseous dental implants (see below). Mostly, these constructions are made of alloys and are often veneered with porcelain. The veneers may complicate the diagnosis of adverse reactions because such restorations can be difficult to distinguish from natural

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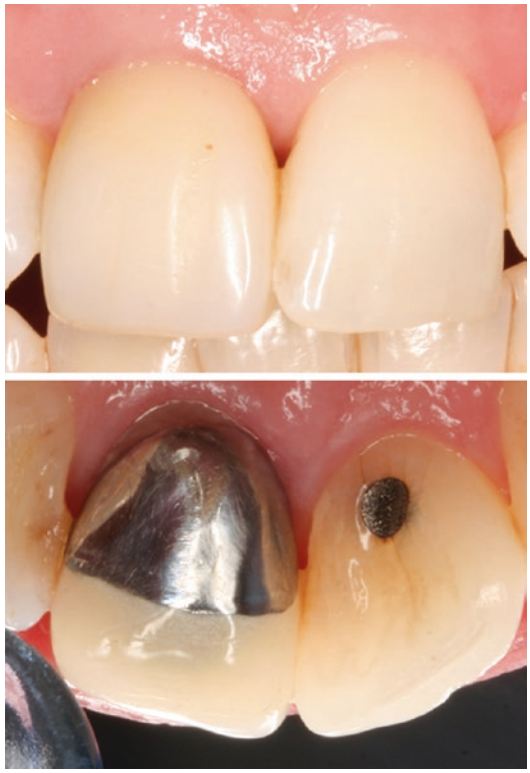

Fig. 22.1 Clinical pictures of buccal and palatal sides of front teeth. The *left element* is restored with a metal porcelain crown. The *right element* is a natural tooth with a small palatal amalgam filling. From a buccal perspective, it is not possible to distinguish the crown from the natural tooth. Of note, often also the palatal part of the crown is veneered with porcelain

teeth (Fig. 22.1). There is a huge arsenal of dental alloys available, which are roughly divided into high-noble, noble and base metals and titanium (Ti) alloys (according to the American Dental Association's revised classification system for fixed prosthodontics (2)) (Table 22.1). High-noble (or gold (Au)-based) alloys largely consist of Au and are mostly alloyed with platinum (Pt), and/or palladium (Pd). The price of these materials is high, and their use is therefore limited. Noble, predominantly Pd-based alloys are usually a composition of Pd with Au, Ag, Cu and/or gallium (Ga). This group of alloys is probably most popular, as they combine fair prices with presumed 'biocompatibility'. Base metal alloys, like stainless steel and nickel-titanium (Ni-Ti) alloys, are mainly used in orthodontics. Still, nickel-chromium (Ni-Cr) and chromium-cobalt (Cr-Co) alloys are abundantly used for FDPs due to their low prices. Ti and its alloys are considered 'biocompatible' and are mainly used for endosseous dental implants and supra-structures.

Removable Dental Prostheses (RDPs) are appliances that replace multiple lost/missing teeth. Complete RDPs (or full/complete dentures) replace all teeth in one jaw and are mostly made of resin-based materials, i.e. polymethylmethacrylate (PMMA). Partial RDPs (or partial dentures) replace one or multiple missing teeth and often consist of a metal base or core structure that is finished with PMMA. They are attached to remaining teeth and/or implants by clamps, 'click systems' or magnets. Such appliances are usually made of Cr-Co alloys (called Vitallium®) or are Ti-based to provide sufficient strength and stiffness. For parts of these constructions, such as mounting bars between implants, other alloys can be used.

Dental implants are basically Ti (alloyed with vanadium (V) and aluminium (Al)) screws anchored in the mandibular or maxillary bone (endosseous). On the implant, a so-called abutment is placed which is usually made of Ti, but other alloys or zirconium (Zr) may be used. The abutment connects the implant with the supra-structure, like a crown/bridge or removable prosthesis, which in turn can be made of a different material (Fig. 22.2).

Orthodontic appliances are used to move teeth to a more functional or aesthetic position within the jaw. Typically stainless steel (316L) is used in combination with flexible alloys like Ni-Ti. Active orthodontic appliances are usually in situ for approximately 2–3 years. However, to retain the treatment result, a retention wire is often placed behind the frontal teeth, which remains in situ for decades. These retainers are commonly made of stainless steel.

22.1.2 Metals Used in Dental Applications

While metals such as Au and Pt were used more extensively in the early twentieth century, their use has been gradually replaced with other metals and Pd, in particular, during the last decades [3]. The choice of metals depends on the purpose

Table 22.1 Classification of dental alloys based on weight percentage according to the American Dental Association (ADA) [2]. Thousands of different dental alloys exist, for which a great diversity of metals is used

Classification	Percentage of noble metals	Subgroups	Most important components
High noble	≥60% Au + Pt + Pd (>40% Au)	Au-based alloys	Au-Pt Au-Pd
		Pd-based alloys	Pd-Au (>40 Au)
Titanium (alloys)	>85% Ti	Commercially pure Ti	Ti (>99%)
		Ti alloys	
Noble	≥25% Au + Pt + Pd	Pd-based alloys	Pd-Au (<40 Au) Pd-Ag Pd-Cu
		Ag-based alloys	Ag-Pd
Base metal	≤25% Au + Pt + Pd	>20% Cr	Ni-Cr
		<20% Cr	Ni-Cr
		Cr-Co (e.g. Vitallium®)	Cr-Co
		Stainless steel[a]	Co-Cr-Ni of Cr-Ni
		Ti alloys	Ni-Ti[a]

[a]Mostly applied in orthodontics; noble metals: gold (Au), palladium (Pd), platinum (Pt); base metals: chromium (Cr), cobalt (Co), copper (Cu), nickel (Ni), silver (Ag), titanium (Ti)

(restoration, implant, orthodontics, etc.), but it also varies significantly between countries depending on the culture, health care system, demand and level of income. Metal-fused-to-porcelain crowns are still the most abundantly used type of dental crowns, although zirconium oxide-based (ceramic) crowns are gaining popularity. Overall, there seems to be an ever-increasing variety of products and alloys produced by the dental industry, and to date thousands of different alloys have been produced. The metal composition of dental work is complex and diverse. It may be difficult to ascertain the composition of dental alloys in individual patients. Consulting the patient's dentist will be helpful. The composition of intraoral alloys may be determined using scanning electron microscopy (SEM) and energy dispersive X-ray analysis (EDAX) [4]. In this so-called microanalysis, a microscopically small sample is taken from the restoration. The most important metals used for dental appliances are summarized below (Table 22.1).

Gold (*Au*) is a noble metal that, due to its soft and malleable properties, needs to be alloyed with metals like copper, platinum and/or Pd. From a dentist's point of view, Au alloys are still the first choice due to their optimal mechanical properties. Gold is one of the least reactive metals. Still, sensitization to Au is frequently observed in patients tested with metal series [5–7]; however, this is rarely relevant for ACD, and its relevance in oral disease is still unclear [8]. Nevertheless, sensitization to Au seems to be related to oral lichenoid lesions [9] and to exposure to dental Au [10].

Platinum (*Pt*) is an important strengthening component of Au alloys. Platinum rarely causes ACD but may play a role in IgE mediated allergy and adverse reactions to drugs.

Palladium (*Pd*) is a noble metal that is widely used in dentistry as a substitute for Pt and Au. Palladium is a hard metal that, like Pt, adds strength to alloys. It has a white appearance and is metallurgically compatible with Au and therefore useful in Au alloys. Dental alloys may consist up to 90 wt% Pd [11–13]. Sensitization to Pd is related to exposure to dental crowns [14] and oral disease [15].

Cobalt (*Co*) is an important constituent of Vitallium®, an alloy trademark (60% Co, 20% chromium (Cr), 5% molybdenum (Mo) and other metals) that is commonly used for metal-based removable dental prostheses. Similar to Ni-Cr alloys, Cr-Co alloys are also used for fixed dental prostheses, especially for financial reasons. Some alloys used in orthodontics may contain Co. There is an ongoing debate whether or not Co allergy has clinical relevance in oral disease [16], as allergic reactions are usually related to consumer products and occupational exposure [17].

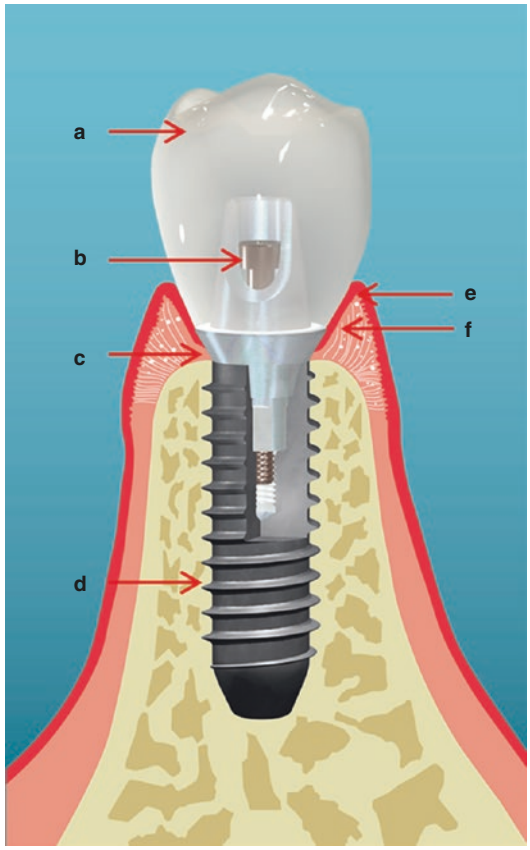

Fig. 22.2 Schematic representation of implant-crown construction in bone and gingiva. (**a**) The dental crown can be made from various materials including metals. (**b**) The abutment screw fixes the abutment to the implant (mostly made of titanium alloy). (**c**) Abutment to support the crown and to connect it to the implant (mostly made of titanium alloy). (**d**) Dental implant in the bone to replace the lost natural root. (**e**) Indicates the dental sulcus (max 1 mm). (**f**) Junctional epithelium towards the bone (1–2 mm)

Chromium (*Cr*) is a part of stainless steel (18–25%) and abundantly used in orthodontics. Furthermore, it is a constituent of Ni-Cr alloys as mentioned above, and Co-Cr-Mo alloys (Vitallium®) are typically used in fixed and removable prostheses in dentistry. Chromium easily oxidizes, resulting in a passivation layer, which prevents corrosion. Sensitization to Cr generally manifests in dermatitis from contact with leather products or occupational exposure [17].

Nickel (*Ni*), like Cr, is a component of stainless steel alloys (8–14 wt%) and is widely used in orthodontics for brackets, headgear and other parts, such as orthodontic retention wires. In contrast to the active orthodontic appliances, retention wires remain in situ for decades or even a lifetime. Nickel is well known to be prone to corrosion, especially in the aggressive oral environment [18]. It has been shown that these retention wires can release great amounts of Ni in experimental scenarios [19] and could also be responsible for extra-oral eczema even in the absence of local reactions [20]. Ni-Cr alloys are still widely used for fixed dental prostheses, especially for financial reasons [18]. Sensitization to Ni is common and clinically relevant in the oral cavity.

Titanium (*Ti*). The vast majority of endosseous dental implants are made of commercially pure Ti (>99 wt%) or its alloys like Ti6Al4V (Ti with 6 wt% aluminium and 4 wt% vanadium). Abutments, used to connect implants to the suprastructures, are also mostly made of Ti or its alloys. Titanium surfaces, even when alloyed, immediately oxidize when exposed to air. This oxidation creates a passive layer, making the metal resistant to corrosion. Still, this passive layer (10–20 nm) can be easily affected by many influences such as mechanical forces, exposure to high concentrations of fluoride and corrosion [21, 22]. Titanium allergy has rarely been identified as an allergen in oral disease using patch testing [23, 24], most probably due to the use of or instant formation of TiO_2 from other Ti test salts, which does not penetrate the skin [25, 26]. Notably, TiO_2 has been shown to penetrate the oral mucosa [27, 28]. In in vitro assays such as lymphocyte proliferation or transformation test assays, (LPT/LTT), sensitization to Ti was frequently diagnosed (4.2–42%), although the clinical relevance of these positive test results is unclear [29, 30]. Still, of 56 patients who developed health problems after dental implant insertion, half showed increased Ti-induced lymphocyte proliferation. Ti-positive patients who had their implants removed showed considerable health improvement [31]. At this time, Ti patch testing is unreliable.

22.2 Corrosion in the Oral Cavity

Corrosion is an inevitable chemical reaction between the oral environment and dental alloys. When an alloy is susceptible to corrosion, large

amounts of corrosion products, i.e. metal ions, are released in the local environment. Further distribution of the metal ions into biological tissues may lead to adverse reactions either locally or systemically. It is important to emphasize that corrosion of dental restorations differs from dental implants. Corrosion products from restorations are released into saliva and may penetrate the tissue, whereas corrosion products from dental implants are released directly into the body by definition.

A well-known example of corrosion of dental alloys is the greyish discoloration of teeth restored with dental amalgam and the marginal breakdown of amalgam restorations. Less known is the corrosion of dental cast alloys that may contain both noble and base metals, such as Ni, Pd, Cr, Co, Au, Ti and many more. Despite the nobility of certain metals, all metals will corrode (to some extent) in the aggressive oral environment [1, 32].

Notably, tarnish is a surface discoloration resulting from hard and soft tissue deposits, like sulphides and chlorides, and is easily removed by polishing. Tarnish does not cause material breakdown. In contrast, corrosion is a chemical reaction and is always accompanied by material breakdown.

The most important difference between corrosion at the skin versus the oral mucosa is the constantly wet conditions of the latter. Saliva contains multiple dissolved oxidisers like oxygen that withdraw electrons from the metal/alloy. The extraction of electrons results in a positively charged metal surface, resulting in the release of positively charged metal ions into the saliva.

Basically, two main localized wet corrosion processes occur in the oral cavity: firstly, galvanic corrosion that is driven by the electrochemical potential between two connected metals or alloys; and second, crevice corrosion that is driven by an oxygen concentration gradient within one metal or alloy. These processes may work simultaneously on one metal or alloy and are further enhanced by the hostile oral environment. Since corrosion processes are described in detail in Chap. 2, here the specific environment of the oral cavity is discussed.

22.2.1 Galvanic and Crevice Corrosion

Galvanic, bimetallic or contact corrosion occurs when two dissimilar metals or alloys are placed in direct contact in the presence of an electrolyte, like saliva or other body fluids. The driving force is the electrochemical potential between the dissimilar alloys. This results in dissolution of the metal at the anode (less noble metal). The free electron will travel through the contact area of the two metals towards the cathode (noble metal) and will there be released into the environment. Thus, the electron exchange occurs through the contact point and the metal ion exchange through the electrolyte. Notably, some alloys are called 'multiple-phase' alloys. Within these alloys, different 'phases', e.g. areas with dissimilar compositions, coexist, resulting in galvanic corrosion within the alloys itself. Obviously, these multiple-phase alloys are more prone to corrosion than single-phase alloys [1, 33]. Clinically, galvanic corrosion plays a role in many situations. Often dental alloys are in direct contact to each other; for example, when an amalgam filling is situated directly next to a gold dental crown. Also, opposing restorations may contact one another during mastication, grinding and clenching. Notably, mechanical wear accelerates corrosion processes due to the local breakdown of the passive layer [34]. Many dental constructions are an assembly of two or three different alloys. For example, a dental crown may be in contact with a core build-up or implant abutment, which again is connected to the implant itself (Figs. 22.2 and 22.3). All three alloys may be of different composition. If the alloys are not in direct contact, galvanic corrosion may still occur since the restorations are connected via the oral tissues and saliva. Of note, the presence of multiple dental alloys in one patient is very common (Fig. 22.4).

Crevice corrosion of a dental alloy occurs in the small sheltered volume of a crevice. Basically, the process is similar to pitting corrosion and is driven by an oxygen gradient between the crevice surface, i.e. a place with a low oxygen concentration, and the bulk surface of the alloy. In a crevice, unstable metal chlorides are formed that tend to hydrolyse, resulting in an increase of H^+ ions.

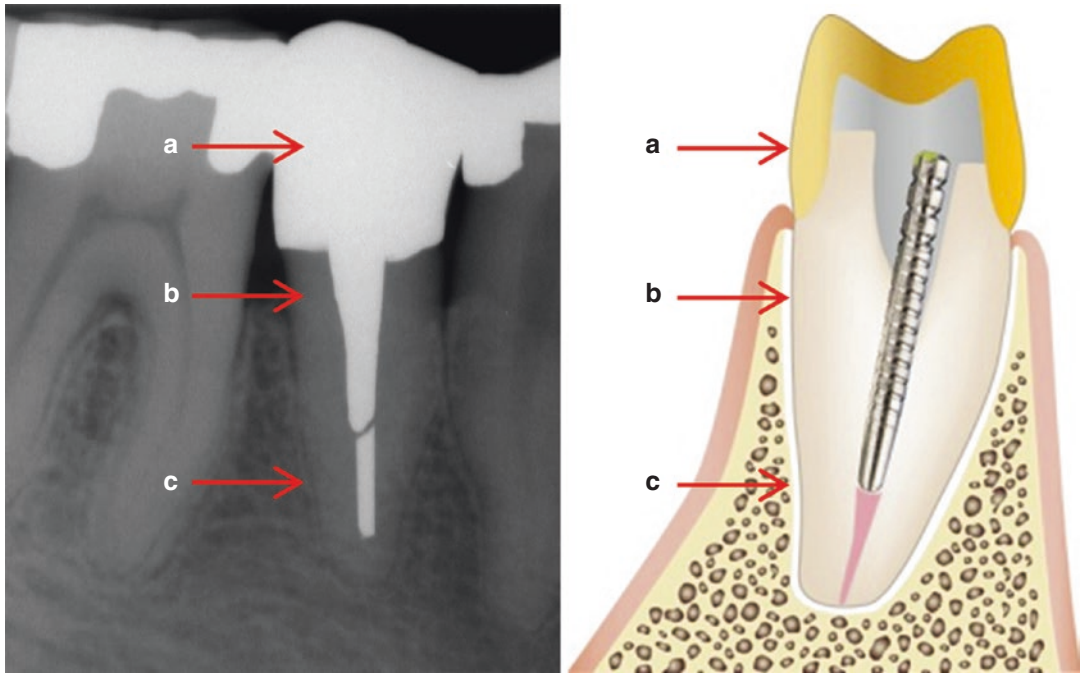

Fig. 22.3 (*Left*) X-ray picture of solitary lower premolar (with parts of neighbouring elements). (*Right*) Schematic representation of the X-ray (©ACTA – Dept. of Oral Implantology and Prosthetic Dentistry). (**a**) Metal-based crown. (**b**) Metal core structure. In some cases, the metal post may be cast onto the core (*right picture*). In that event, two different alloys are cast to each other. This is radiographically not visible. (**c**) Silver point of root canal filling

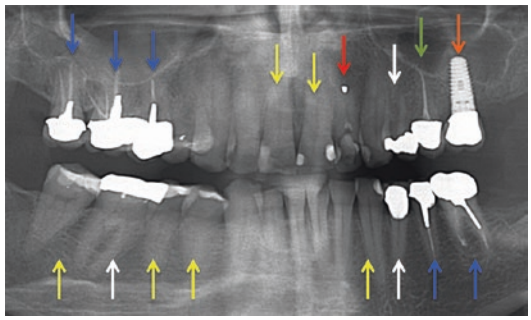

Fig. 22.4 Ortho Pantomo Graph (OPG; X-ray) showing the upper and lower jaw with teeth and molars from one patient. *Yellow arrows* indicate elements with resin composite filling. *White arrows* indicate elements with metal-based dental crowns. *Green arrow* indicates element with root canal filling and metal-based crown. *Blue arrows* indicate elements with root canal fillings, metal core and metal-based crown. *Red arrow* indicates element with retrograde root canal filling, in this case amalgam (small *white spot* at the apex of the root). Of note, theoretically all these metal structures could be composed of different alloys

This acid environment further accelerates the corrosion processes. Examples of crevices in the oral cavity are propagated pits, scratches in the alloys due to wear or insufficient finishing in the dental laboratory, interdental spaces or close contact areas between different parts of the restorative structures.

There is a specific oral microenvironment where crevice corrosion has a particular biological impact. Dental restorations or crowns often extend below the level of the gingiva into the gingival sulcus. This is a physiologically occurring sulcus or crevice. It is the interface between a tooth and the surrounding gingiva (Fig. 22.2). The oral tissues are here coated with the sulcus epithelium that has great similarity with the gingiva, being a stratified squamous keratinized epithelium. Further towards the apex of the dental root, at the base of the gingival sulcus, lies the so-called junctional epithelium (JE), providing the ultimate transition from the outside to the inside of the body. The JE maintains a tight seal against the mineralized tooth surface, i.e. enamel, with hemi-desmosomes, called the 'epithelial attachment'. It tapers off in the apical direction and consists of 15–30 cell layers coronally and only 1–3 cell layers at the cement-enamel junction [35]. It is a stratified squamous non-keratin-

ized epithelium that is made up of two strata only: a basal layer and supra-basal layer; it lacks membrane-coating granules and is therefore highly permeable and assumedly much more permeable than the floor of the mouth. As the cells are interconnected by a few desmosomes only, the intercellular spaces are relatively wide, allowing for fluid secretion and transmigration of leucocytes. These leucocytes form the basis for the crevicular fluid, which comprises the first line of peripheral host defence against the bacteria in this area. In a situation of inflammation, the epithelial attachment may be lost, or the JE may even get disrupted due to either increased fluid flow or bacterial products and leucocytes passing through [35]. The JE has been shown to be permeable to a variety of materials ranging from carbon particles [36] to proteins [37], especially when the tissue is inflamed. Importantly, the underlying connective tissue has a dense capillary network, which assumedly helps corrosion products to enter the bloodstream.

22.2.2 Patient Factors

Unlike the skin, the mouth comprises an ideal environment for corrosion processes to occur. The constant presence of saliva, with corrosive compounds like hydrogen, chloride ions, sulphide compounds, dissolved oxygen and free radicals, enhances the corrosion of dental appliances, which in turn leads to metal exposure. Consumption of foods and beverages results in constant fluctuations in acidity (pH 1.5–8.0) and temperature (0–60 °C), which also contributes to corrosion processes. Especially Ni release from dental alloys is greatly enhanced by pH values between 1–4 [32, 38]. For example, cola has a pH around 1.5, but also fruit juices are commonly acidic. The presence of proteins like serum albumin was also found to increase elemental release from dental alloys [39, 40]. Serum albumin plays a fundamental role in the distribution of transition metals, including Pd, in the human body [41].

Individual general health aspects may also play a role in corrosion processes. For example, it is well known that xerostomia, independent of its aetiology (such as Sjögren's syndrome or as an adverse effect of many pharmaceutical drugs), decreases the saliva's pH and its buffering capabilities [42]. Hypertension has also been linked to decreased pH in unstimulated saliva [43]. Oral hygiene can also enhance corrosion. For example, fluoride ions, a key element in cavity prevention, are known to attack the passive oxide layers of Ti, Cr and Co alloys in vitro, when concentrations rise above the range of 0.05–0.2% [22]. Furthermore, it has been shown that tooth brushing also increases metal ion release, especially when abrasive toothpaste is used [44–46]. Inversely, no tooth brushing also enhances corrosion as it was found that *Streptococcus mutans*, a lactic acid-producing bacteria and the primary contributor to dental decay, colonizes within 24 h Ni-Cr alloys. Due to the lactic acid production of these bacteria, the metal ion release was increased, causing cytotoxic and pro-inflammatory cell responses [47]. On top of that, accumulation of dental plaque will promote crevice corrosion due to local low oxygen availability.

22.2.3 In Vivo Ion Release and Uptake

Although the mechanisms of corrosion are theoretically well known, due to individual, clinical and alloy-production-process variables, the exact in vivo corrosion mechanisms remain complex, and it is difficult to obtain reliable figures on in vivo metal ion release. The oral tissues do not absorb most of the released ions, as they are diluted by saliva. Still, as dental restorations often extend below the level of the gingiva within the gingival sulcus, micro-environments are formed where ion concentration can reach high levels due to the absence of saliva [1]. Moreover, biologically adverse effects can be enhanced due to direct cell contact [48]. It has been clearly shown that exposure to dental amalgam is associated with increased levels of Hg in blood, plasma, urine and body organs as compared to people with no dental amalgams [49, 50] and that urinary Hg levels decreased after amalgam removal to levels similar to those of patients who never had an amalgam filling [51, 52].

Furthermore, some reports provide evidence for considerable absorption of released metal ions from high-noble or noble dental alloys. Significantly higher levels of Au and Pd were found in gingival tissues adjacent to dental cast restorations compared to control groups [53]. Cristaudo et al. found significantly higher concentrations of Pd in saliva, blood serum and urine in six patients with Pd-containing dental restorations relative to negative control groups [54]. Drasch et al. found that the Pd and especially the Au content of body fluids, i.e. resting saliva, chewing saliva, serum, whole blood, morning urine and faeces, were correlated to the number of high-noble or noble dental alloys. The calculated maximum of Au and Pd in one day's saliva of 1.38 mg and 70 μg, respectively, was found. They concluded that for Pd, the composition, rather than the number of restorations, might be the critical factor for ion release with subsequent increased concentrations of Pd in body fluids [55]. It has been calculated that exposure to Pd in the general population is mainly caused by dental restorations [56], and Pd-based dental alloys were shown to release up to 80 ng cm^{-1} per day in artificial saliva [57–59]. Likewise, for Au, the number of Au-based inlays (*indirect fillings*) is related to the concentration of Au in the blood, even after many years [55, 60]. Furthermore, it has been reported that the Au concentration in blood positively correlates to patch test reactivity [61, 62].

A final remark in this context should be made. The production process in the dental laboratory importantly influences the in vivo release of metal ions. The casting process itself has been shown to double the Pd release from Pd-Ag alloys [63]. Then, during the veneering process, corrosion resistance may further drop [64]. Also, reuse of casted alloys may be insidious to the corrosion resistance [65]. Most of the literature on corrosion resistance of dental alloys investigated the alloys that were directly obtained from the manufacturer, which can be misleading for the in vivo situation.

In summary, the complex corrosion processes occurring in the oral cavity are difficult to quantify in vitro and in vivo. Still, it is fair to say that substantial metal ion release will take place for all dental alloys, and some, including Au and Pd, will be at least partially absorbed by the body. Furthermore, corrosion is a continuous process that increases with time, especially in the case of crevice or pitting corrosion. It is well established that the release of Ni from dental casting alloys is most common.

22.3 Adverse Reactions to Dental Alloys

Norway, Sweden and the United Kingdom have national reporting systems for adverse reactions to dental materials. In the USA, such a system is executed by the Food and Drug Administration (FDA), although it is a part of MedWatch [66] and, as such, also records reports about the malfunction of dental devices [67]. An overview of the data obtained from European reporting systems showed that patients with subjective and objective complaints attributed to their dental materials were 70–80% female, and the most commonly affected age groups were 40–49 and 50–59 years of age for both men and women. Similar data was found in Tokushima, Japan [68]. The vast majority of the reports concerned dental alloys [69].

Nearly all metals used in dental alloys may cause hypersensitivity in humans; the most common ones are Ni, Cr, Co, Pd, Au, Ti and Hg. Especially for dental crowns and bridges, a huge arsenal of alloys are available on the dental market, all using different compositions. Of all metals, Au and Pd are of special interest in this context. When exposed to the skin, like in jewellery, these noble metals have good resistance to dry corrosion, and, therefore, they are well tolerated even in hypersensitive patients. In the aggressive oral environment, however, these metals will corrode, leading to possibly relevant exposure. Indeed, particularly hypersensitivity to Au and Pd has been associated with dental alloys and subsequent adverse oral reactions [10, 14, 70–74].

Palladium is known to cross-react with Ni [75–80]. When with patch testing instead of $PdCl_2$ the more sensitive test allergen (Na_2PdCl_4) is used, it becomes clear that cross-reactivity between these metals is not absolute, and about

25% of the Ni and Pd sensitized patients are mono-sensitized to both metals [81–83]. In contrast to Ni, Pd sensitization is not associated with the female gender, suggesting a different source of exposure [81]. Palladium and not Ni mono-sensitization is related to exposure to dental alloys and dental crowns in particular [14, 15, 17, 56]. Interestingly, in a European multicentre study, it was shown that from 906 dermatology patients with dental alloys (n = 496), 44% suffered from metal ACD, in comparison to only 28% of dermatology patients without dental alloys (n = 410) [14]. For those patients with dental crowns, the percentage was even higher, i.e. 52%. Perhaps exposure to dental alloys could lower the patient's threshold for elicitation via the skin, or systemic ACD could play a role. Not only is Ni widely used in dental alloys, oral Pd exposure could lower the threshold for Ni elicitation in the case of cross-reactivity.

Both local and systemic symptoms have been attributed to adverse reactions to dental alloys in the scientific literature [14, 70, 72, 84, 85]. However, none of these are specific or pathognomic manifestations [7, 86–88] nor is it clear whether these reactions result from innate immune responses or hypersensitivity to specific metals in dental alloys. Importantly, diagnostics may also be blurred by tolerogenic immune responses of the oral mucosa.

22.3.1 Innate Immune Responses

Nickel ($NiCl_2$), palladium (Na_2PdCl_4) and cobalt ($CoCl_2$) have been shown to induce innate immune responses by triggering TLR4 on human monocyte-derived dendritic (MoDC) cells measured by elevated pro-inflammatory cytokine IL-8 release [89, 90]. Gold ($Na_3Au(S_2O_3)_2.2H_2O$) was found to induce substantial IL-8 release by triggering TLR3 from MoDC, PBMC and THP-1 cells [91] on both skin- [92, 93] and gingiva-derived keratinocytes [94]. Subsequently, it was shown that ionized Au was a strong innate activator of human keratinocytes [94]. Thus, epithelial TLR3 is likely to play a key role in both skin- and mucosa-localized irritation reactions to Au.

Human MoDC and THP-1 cells were cultured on top of different dental alloy specimens (Ni-Cr, Co-Cr, Pd-Cu, Pd-Ag, Ti-6Al-4 V, amalgam, Au-alloy and stainless steel). All dental alloys induced significantly elevated IL-8 production in both MoDC and THP-1 (except for Cr-Co) cells, with Au and Pd-Cu providing the strongest stimulation. Even in 24 h alloy-exposed non-corrosive culture media, all alloys, except Ni-Cr and stainless steel, resulted in significantly elevated IL-8 production [95]. Also, Au, Pd-Cu, Pd-Ag, Ti-6Al-4 V and amalgam were effective in potentiating LPS responsiveness [95]. These findings might explain why oral exposure to Au-, Pd- and Ti-based dental alloys is associated with local non-dental plaque related inflammatory responses in the absence of hypersensitivity.

22.3.2 Tolerogenic Immune Responses of the Oral Mucosa

Oral mucosal DCs have a unique repertoire of receptors that induce tolerance rather than inflammation [96]. They express high affinity receptors for IgE that upon ligation lead to IL-10 and TGF-β production, which is necessary for the induction of Tregs [97]. Also, oral DC activation by TLR-4 (by LPS) will induce Tregs expressing FOXP3, IL-10 and TGF-β [98]. Oral DCs express constitutively more B7.H co-inhibitory molecules and thereby contribute to immune-silencing [98]; their expression is up-regulated by ligation of TLR-4 [97]. B7.H inhibits T-cell activation through binding with CD28.

The clinical outcome of these tolerogenic properties of the oral mucosae is observed in patients who had orthodontic treatment or oral exposure to Ni prior to ear piercing, resulting in decreased levels of sensitization to Ni compared to ear-pierced patients without previous orthodontic treatment [99, 100]. In a guinea pig study, it was shown that oral tolerance resulted from antigen-specific immunosuppression and was induced more effectively after direct contact with the oral mucosa (using an ointment) than via feeding [101]. In a murine study, tolerance to Ni was effectively achieved by intra-gastric feeding

of Ni [102]. Even Ni-releasing cages and drinking nipples were sufficient to induce tolerance for this metal in mice [102].

Another important factor that influences immune response is age. From studying the skin, it is known that the number of DCs decreases with age, possibly in response to UV exposure. Even though UV exposure is not likely to occur in the oral cavity, a considerable decrease in DCs was still reported in subjects older than 40 [103], which might be why oral diseases are more frequently observed in the elderly. The induction of oral tolerance was found to be less effective in older guinea pigs compared to younger animals [101].

Finally, effector T cells are strongly biased towards skin migration rather than towards mucosal surfaces [104, 105]. This may explain the systemic complaints from hypersensitivity to dental alloys in absence of local symptoms or lesions as illustrated by several case reports [20, 106–109]. One report describes a 54-year-old Taiwanese woman who suffered from full-body annular erythema for 15 years; her condition was alleviated almost immediately after one Pd-containing dental inlay was removed. No flare-up reactions occurred for 2 years following [108]. A Japanese retrospective study reported that in patients suspected of having an allergy to metal in dental alloys, pustulosis palmaris et plantaris/dyshydrotic eczema and contact dermatitis were frequently found (±30%). Also in these cases, mostly no intraoral signs of contact allergy were visible [68]. It is clear that the absence of local clinical signs of hypersensitivity to dental alloys may be a major pitfall in its diagnosis.

22.3.3 Objective Symptoms

Lichen planus is a chronic systemic disease of established (auto) immune-mediated pathogenesis. It commonly involves the oral cavity, but it may involve other sites such as the skin, vaginal mucosa, glans penis, the scalp (alopecia) and the nails [110]. Some cases have been described in which alopecia in patients with positive patch test results for Ni and Pd disappeared after the removal of Pd and/or Ni-containing dental restorations [111]. The author explained the pathogenesis by the high affinity of these metals for binding to the sulphur (-SS-) in hair follicles and referred to this phenomenon as ‘internal contact dermatitis’. Oral lesions are mostly bilateral and symmetrical, characteristically with a lace-like network of slightly raised grey-white lines (Wickham’s striae). The lesions may be reticular when Wickham’s striae are present; the plaque-like form is similar to leukoplakia. In the case of erythematous/erosive oral lichen planus (OLP), mostly the gingiva is affected. It is unlikely that sensitization to metals plays a significant role in the aetiology of OLP.

Clinically and histopathologically, OLP may be indistinguishable from oral lichenoid lesions (OLL). OLL result from contact with dental materials, as a result of drug reactions or from graft versus host disease [112]. Dental materials most commonly related to OLL are amalgam, Au and Pd [8, 9, 14, 70, 113–115]. The lesions are usually in close contact with the causative dental material(s). It is not fully clear whether or not OLL results from a type IV allergic reaction, as the value of patch testing has been debated [14, 70, 71, 88, 116–118]. From this perspective, OLL may be a manifestation of irritant contact stomatitis [94, 95, 118]. Still, a positive patch test to a metal of the dental alloy and a strong topographic association between the lesion and restorative material are positively correlated, and the lesions generally disappear after the alloy is removed [119, 120]. Other allergens, such as perfumes, cinnamaldehyde (in cinnamon), carvone (in caraway and dill) and other food additives are also related to OLL [7, 86, 88]. In the scientific literature dealing with adverse reactions to dental alloys, the distinction between OLP and OLL is often not made or not well described.

A variety of symptoms and lesions have traditionally been associated with dental alloys; however, most studies report on small numbers, making it difficult to draw definitive conclusions. Most reported lesions/complaints attributed to metals are stomatitis and gingivitis/bleeding and/or swelling of the gingiva and are similar to inflammatory responses to bacteria. Also, in the case of non-plaque-related gingivitis in direct contact to metal-containing restorations, the

diagnosis of contact hypersensitivity is very often not made [70], suggesting again innate immune responses [95].

Finally, it has been reported that referring dentists often overlook intraoral lesions, since many more lesions have been reported by specialists in the field, such as those working in adverse reaction units [121]. This could mean that general dentists and dermatologists are under-reporting oral lesions. In this context, it is noteworthy to stress that dental metal-based crowns and bridges are often difficult to distinguish from natural teeth as they are mostly veneered with porcelain.

22.3.4 Subjective Symptoms

22.3.4.1 General Complaints

Several studies report on decreased health complaints after the removal of amalgam fillings [50, 121–125]. The most commonly reported complaints that improved after restoration replacements were pain from muscles and joints, memory and concentration problems, complaints about the ear/nose/throat and fatigue. However, treatment without removing the offending amalgams was also found to significantly reduce the symptoms [124]. Furthermore, these complaints are also frequently observed in the general population, although the intensity of the complaints is lower [122, 123]. Stejskal et al. [126] studied the relation between dental alloys, various subjective complaints and lymphocyte transformation test results. They reported significantly increased Pd-, Au- and Hg-induced lymphocyte proliferation in 111 chronic fatigue-like patients compared to 116 controls. Of those 111 patients, 98 had their dental restorations removed, and 76% (n = 83) reported long-term health improvement. Interestingly, during a follow-up, 73 patients who removed their dental alloys were retested and showed dramatically reduced lymphocyte proliferation of the aforementioned metals. Of note, in these patients Ni-induced proliferation was not reduced. Several interesting cases have been described in more detail [127]. It has been suggested that ongoing chronic inflammation with subsequent increased cytokine levels may affect the hypothalamic-pituitary-adrenal axis (HPA axis), triggering non-specific somatic and psychological symptoms [126].

It may be concluded that there is only scarce evidence suggesting improvement of systemic complaints as a result of dental alloy removal and that several other factors must be taken into consideration, especially psychosomatic factors [50, 128].

22.3.4.2 Local Complaints

The most commonly reported subjective local complaints are burning mouth/tongue, metallic taste/taste disturbance and/or dry mouth [72, 122, 123]. However, there is little evidence for true associations with allergy to dental alloys, in particular, for burning sensations/burning mouth syndrome (BMS) [14, 129]. The exact aetiology of BMS remains imprecise and is likely multifactorial, including neuropsychiatric, endocrine, immunologic, nutritional, infectious and iatrogenic causes [130]. In the context of immunologic aetiologies, also food allergens can be involved [7]. Xerostomia has been related to exposure to dental alloys and to hypersensitivity to Ni and Pd [14]. However, many drugs also induce xerostomia and/or taste disturbance and may present further confounding variables [131, 132]. Metallic taste is primarily a sign of exposure due to corrosion. The lack of evidence for an association with allergy does not exclude an association with exposure. Indeed, metallic taste has been related to exposure to dental alloys [14]. Notably, burning sensation and xerostomia are probably related, since in the case of xerostomia, the mucin layer, with its important barrier and protective function, is absent, resulting in increased susceptibility to irritation/burning sensation from otherwise harmless food components and/or additives.

Another important issue to address is the possible influence of menopause on oral health. The female population within the age range of 40–60 is the largest patient group afflicted by oral disease attributed to dental materials. Periodontal disease, burning mouth syndrome and xerostomia are common manifestations in postmenopausal women [133]. The density of important immune-regulating cells was found to

be drastically reduced in gingival tissues of healthy subjects older than 40 relative to those under 40, a finding that contributes to the predisposition for oral disease in the older population [103].

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23 Hypersensitivity to Other Implants: Gynecological, Neurovascular, Oculoplastic, Nuss Bars

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23.1 Introduction

In this chapter, we will describe the use of a diverse group of medical implants that are utilized in a variety of medical fields, as well as in different patient populations with varying disease states (i.e., congenital deformities, vascular malformations, nerve palsies) or medical needs, such as contraception in healthy young women. Additionally, there are a number of different metals utilized in this diverse set of metal implants. It is, therefore, not surprising that hypersensitivity reactions to such implanted metals may range from either nonexistent or very rare to serious adverse reactions. Thus, this remains a major consideration in preoperative decision making or postoperative management of the patient with potential complications related to an implanted device. It is noteworthy that the epidemiology of hypersensitivity reactions to some of these metal implants is not well studied, with population studies lacking to define the role of predictive patch testing in preimplantation decision making. Medical implants utilized for gynecologic applications are utilized predominantly for contraception. Neurovascular implants (coils, clips, and stents) are utilized for the treatment of intracranial aneurysms, a potentially life-threatening condition. Oculoplastic implants are utilized as a pessary to treat lagophthalmos, related to cranial nerve palsies. Lastly, Nuss bars are used to surgically correct pectus excavatum, a congenital thoracic cage deformity. Considering the wide range of conditions for which these metal implants are utilized and the diverse anatomic compartments where these implants are placed, there are very specific issues related to each of these implants.

23.2 Gynecological Implants

Copper, nickel, and titanium are found in various implantable devices used for female contraception. The Essure micro-insert is made of a nickel-titanium alloy and is permanently implanted in the fallopian tube. Non-hormonal intrauterine devices are made of copper and may be implanted in the uterus for a period of up to 10 years.

23.2.1 Essure

The Essure (Conceptus, Mountain View, CA, USA) micro-insert is a hysteroscopically placed, permanent birth control device made of a nickel-titanium alloy (nitinol) outer coil surrounding an inner coil made of stainless steel and polyethylene fibers. Once the device is placed into the fallopian tube, the polyethylene fibers elicit benign

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local tissue ingrowth that results in permanent tubal occlusion after approximately 3 months [1].

Nitinol is a nickel-titanium alloy containing variable proportions of each metal in different implantable devices. It is commonly used in medical devices such as inferior vena cava (IVC) filters, dental devices, intravascular stents, and septal occluders because of its exceptional shape memory and biocompatibility [2]. By weight, the nitinol alloy used in the Essure micro-insert is comprised of 55.8% nickel, 44% titanium, and 0.25% chromium [3]. Once in the biological environment, implanted devices containing nitinol undergo corrosion resulting in the release of nickel that may lead to hypersensitivity [4]. To minimize nickel ion release, Essure is manufactured using a chromium-doped nickel-titanium alloy that is processed so that the entirety of the alloy surface is coated with a protective layer of titanium oxide [3].

The amount of nickel leaching that occurs from nitinol devices has been studied in vitro. When compared to other nickel-containing alloys, nitinol tends to have low levels of nickel leaching (0.14 micrograms/day, approximately 2143 times less than the average human daily intake from food and water) [3, 5]. Data from the US Food and Drug Administration (FDA) in 2012 demonstrated that the release of nickel from Essure micro-inserts is similar to or less than the amount released from other nitinol-containing devices used for cardiovascular implants [6–8].

Nickel allergy is the most common metal allergy and, when patch testing is performed, the most common positive allergen [9]. Considering that significant risk factors for developing nickel sensitivity are female gender and young age, nickel allergy is particularly relevant to the patient population undergoing placement of Essure micro-inserts. Despite there being no reported cases of nickel or metal allergy identified in Phase II or Pivotal clinical trials, post-marketing surveillance suggests that, although uncommon, nickel hypersensitivity may occur after placement of Essure devices [10].

In 2011, Zurawin and Zurawin [3] performed a study looking at adverse events due to suspected nickel allergy in patients with Essure micro-inserts. They performed an analysis of the Manufacturer and User Facility Device Experience (MAUDE) database from 2001 to 2011 along with data from Phase II and Pivotal clinical trials. At that time, 436,937 Essure kits had been sold, and 63 reports of nickel allergy were identified (rate of 0.014%). Considering nickel allergy affects approximately 17% of women [11], these data suggest that the Essure micro-insert has low allergenic potential. Furthermore, a retrospective cohort review reported Essure implantation in 25 women with known nickel allergy, proven by patch testing. None of these patients developed any adverse effects [12].

Although the incidence is low, there are cases reported in the literature that convincingly support device-related nickel hypersensitivity after Essure insertion. One cohort study reported two cases of nickel allergy out of 4306 patients with Essure micro-inserts. These patients developed symptoms of systemic contact dermatitis (i.e., urticaria, erythema, pruritus) after undergoing the procedure for Essure placement, and both women had resolution of symptoms after its removal [13]. Al-Safi, Bibas, and Lane have all reported separate cases of women developing symptoms of rash, pruritus, or edema that occurred after Essure placement and resolved after removal. Additionally, the women reported in these cases all had positive patch testing to nickel [9, 14, 15].

Although patch testing with 2.5% or 5% nickel sulfate is the standard for diagnosis of nickel allergic contact dermatitis, patch testing is not always a reliable predictor of a systemic nickel allergic reaction [3, 16, 17]. Results of patch testing cannot always be deemed clinically relevant, as many patients who test positive on skin patch testing show no clinical signs or history of nickel hypersensitivity, and many patients that report hypersensitivity symptoms to nickel actually test negative with patch testing [3].

Furthermore, it is unknown whether adverse reactions to implantable metal devices are due to a specific cellular immune response [18]. Although it is presumed that implant-related allergy is a type IV hypersensitivity reaction, confirming this mechanism would require biopsy of the affected tissue showing effector T cells and macrophages, which has not been reported [19]. Because the relationship between cutaneous allergy and systemic reaction is unknown, positive patch testing to nickel should not be an absolute contraindication to the use of implantable devices containing nickel [19].

When Essure was first launched, the manufacturer listed nickel allergy as a contraindication for placement, but this has since been removed [20, 21]. Currently there is a label warning that some patients may have an allergic reaction to the nickel in the device and that some patients may develop an allergy to nickel after the device is implanted [21].

There is no consensus on how patients with known nickel hypersensitivity should be managed when considering Essure as a method of contraception. Currently there is no proven method to predict which individuals will develop an adverse reaction to their implant [16]. Although nickel hypersensitivity is not a contraindication per se, there are documented cases of implant-related hypersensitivity reactions. Considering the availability of alternative permanent contraceptive methods that do not involve nickel-containing devices, patients with a history of nickel allergy may choose to avoid this risk, however small it may be. Table 23.1 summarizes published evidence related to hypersensitivity reactions to Essure.

23.2.2 Copper IUD

Copper-containing intrauterine devices (IUD) are frequently used for reversible contraception. The Paragard 380A IUD, the only copper-containing IUD with FDA approval in the USA (Duramed Pharmaceuticals, Tonawanda, New York, USA), contains a 99.9% pure copper wire with polyethylene and barium sulfate [22]. Although copper is a relatively weak sensitizer when compared to other metals, copper can induce clinically relevant allergic reactions, particularly when involving systemic exposure through mucosal surfaces as it occurs with dental devices and IUDs [23, 24]. This biological environment results in the oxidation of copper and release of free copper ions [24]. Copper-containing IUDs have been reported to release copper at a rate of approximately 17–45 micrograms/day [25].

There have been multiple case reports of women developing systemic allergic contact dermatitis after insertion of copper IUDs. Barranco [26] and Rongioletti [27] both describe cases of women presenting with eczematous dermatitis erupting after placement of a copper IUD. The patients were then found to have positive reactions when patch tested with copper sulfate and subsequent resolution of symptoms after removal of the IUD [26, 27].

Hypersensitivity to a copper IUD has also been reported to manifest as angioedema and widespread urticaria [28] and perimenstrual dermatitis [29]. Both of the women reported in these cases demonstrated positive reactions to copper sulfate when patch testing was performed and experienced improvement of their symptoms after the IUD was removed.

Allergy to any of its components is a contraindication to using the Paragard IUD. In a small subset of women, copper allergy may be clinically relevant, and opting for a non-copper IUD would be optimal for them. This is a limited patient population, as copper allergy in the general population is exceedingly uncommon. Considering IUDs that contain copper have been used for over 45 years [30] and only a handful of case reports of sensitivity have been noted in the literature, it can be inferred that, even when accounting for some level of underreporting, hypersensitivity to copper IUDs is a rare occurrence, and there is no role for screening patch testing to be performed in women interested in this form of contraception. Table 23.2 summa-

Table 23.1 Gynecological implants: Essure

Study	Reference number	Patient (s)	Preoperative patch testing	Postoperative complications	Management and outcome
Zurawin and Zurawin (2011)	[3]	63 reports of suspected nickel hypersensitivity identified from 2001–2010 out of 436,927 total kits sold	None performed	Group A: Rash, itching, exacerbation of asthma, leg swelling, and nausea Group B: Arthritis, pelvic pain, rash, and hives Group C: Nausea, shivering, and pain Group D: Pain, hives, and rash	20 patients underwent patch testing; 9 of 13 had a positive reaction to nickel Group A (4 patients): Experienced resolution of symptoms after device was removed Group B (2 patients): Did not experience resolution of symptoms after device removal Group C (2 patients): Status of symptom resolution after device removal is unknown Group D (1 patient): Patient was treated with diphenhydramine and exhibited symptom improvement prior to device removal
Povedano et al. (2012)	[13]	Single center study reporting 2 cases of suspected nickel allergy out of 4306 patients with Essure devices	None performed	One woman, with history of atopy, presented with papular urticaria and erythema developing shortly after implantation; another woman experienced persistent generalized pruritus 1 year after placement	No postoperative patch testing performed Both patients had resolution of symptoms after removal
Al-Safi et al. (2011)	[9]	27-year-old female with no definitive history of metal allergy (patient-reported itching when she wore a halter top with a metallic wire around the neck in the past, but no reactions to jewelry, watch straps, or belts)	None performed	Generalized pruritus and intermittent nausea 3 days after Essure procedure	Postoperative patch testing positive for nickel and nitinol Symptoms resolved after removal of the device
Bibas et al. (2013)	[14]	40-year-old female with self-reported history of jewelry intolerance since adolescence	None performed	Severe anogenital pruritus, erythematous macules, and papules predominantly in genital and flexural distribution	Patient had no relief with topical corticosteroids, oral antihistamines, and systemic corticosteroids Postoperative patch testing was positive to nickel sulfate Implant removal resulted in resolution of symptoms

Table 23.1 (continued)

Study	Reference number	Patient (s)	Preoperative patch testing	Postoperative complications	Management and outcome
Lane et al. (2016)	[15]	27-year-old female with no known history of nickel allergy	None performed	Within days of implantation, patient developed pruritic macules and papules as well as urticaria on pelvis; she intermittently experienced similar symptoms at distant sites such as the neck and axillae and had several episodes of facial edema	Further questioning revealed previous reactions to jewelry, metal buttons, and piercings Postoperative patch testing to nickel was positive Oral prednisone only provided temporary relief Symptoms resolved after device removal

Table 23.2 Gynecological implants: Copper IUDs

Study	Reference number	Patient	Preoperative patch testing	Postoperative complications	Management and outcome
Barranco (1972)	[26]	26-year-old female with no history of metal allergy	None performed	2 weeks after copper IUD placement, she developed pruritic, diffuse, erythematous macules, and papules, beginning on her arms and spreading to her trunk and legs; she also developed urticarial lesions weeks after her initial eruption	Pt had poor symptom control on topical, intramuscular, and oral corticosteroids as well as diphenhydramine Patch testing to 5% copper sulfate was positive Symptoms resolved 4 days after IUD removal
Rongioletti et al. (1985)	[27]	35-year-old female	None performed	Vaginitis and eczematous dermatitis on trunk and limbs several weeks after insertion of copper IUD	Postoperative patch testing was positive to copper sulfate All lesions and symptoms subsided after IUD was removed
Purello D'Ambrosio et al. (1996)	[28]	32-year-old female with copper IUD	None performed	Widespread urticaria, angioedema of eyelids, and labia majora and minora	Corticosteroids and H1 antagonists only provided intermittent relief Post-op patch testing with 1%, 0.5%, and 0.01% copper sulfate was positive In vitro lymphocyte stimulating test with copper was positive with typical crescendo reaction Removal of IUD resulted in resolution of all symptoms

(continued)

Table 23.2 (continued)

Study	Reference number	Patient	Preoperative patch testing	Postoperative complications	Management and outcome
Pujol et al. (1998)	[29]	41-year-old female with history of cholinergic urticaria	None performed	2 years of episodic, non-pruritic, erythematous papules on upper trunk, neck, and arms associated with abdominal distension and cramps occurring cyclically 3–7 days prior to her menses and self-resolving with onset of menstrual bleeding	Postoperative patch testing positive for nickel sulfate and copper sulfate (2%) Abdominal symptoms immediately resolved after removal of IUD, while cutaneous symptoms gradually improved before completely remitting

rizes the published evidence related to hypersensitivity reactions to copper IUDs.

23.3 Neurovascular Implants

There are a variety of neurovascular implants used to treat intracranial pathology, including aneurysm clips, endovascular coils, and intracranial stents. These implants are primarily utilized to treat ruptured and un-ruptured cerebral aneurysms but are also implemented to treat intracranial vessel atherosclerotic lesions and dissections. Ruptured and un-ruptured cerebral aneurysms can be treated surgically with craniotomy and placement of surgical clips or via a minimally invasive technique with endovascular occlusion with coil embolization. Surgical management involves placement of a clip across the neck of the aneurysm to exclude it from circulation. During endovascular occlusion of an aneurysm, detachable coils are deployed into the aneurysm to decrease or stop blood flow into the aneurysm [31]. Intracranial stents have been shown to be a safe and effective technique for revascularization in intracranial vessel disease secondary to atherosclerosis and dissection [32–36]. These stents have also been shown to be effective in treating cerebral aneurysms via stent-assisted coiling, specifically for wide-necked and fusiform aneurysms [37–39]. The stent is placed within the artery from which the aneurysm arises, preventing blood flow into the aneurysm [40, 41].

The prevalence of cerebral aneurysms in the United States (US) is estimated to be between 1 and 8% [31]. Recent studies have investigated the implications of these aneurysms and have begun to understand the natural history of symptomatic un-ruptured and ruptured cerebral aneurysms. Symptomatic un-ruptured intracranial aneurysms carry a 6% risk of rupture each year [31]. The incidence of subarachnoid hemorrhage from a ruptured intracranial aneurysm in the US is about 1 per 10,000 people [31]. The 30-day mortality rate of subarachnoid hemorrhage secondary to a ruptured intracranial aneurysm is about 45%, and 30% of survivors will have moderate to severe disability [31]. Ruptured cerebral aneurysms have a 2–4% risk of hemorrhage within the first 24 hours and a 15–20% risk of re-bleeding within the first 2 weeks [31]. These re-bleeding events are associated with a worse prognosis following intracranial aneurysm rupture. Therefore, in order to decrease the morbidity and mortality associated with ruptured intracranial aneurysms, it is important to detect and to institute early treatment after rupture to prevent further damage. The natural history of un-ruptured asymptomatic aneurysms continues to be elucidated. The risk of rupture is less certain, but studies have estimated the risk to be anywhere between 0.05 and 2% each year [31]. The decision to observe versus

electively treat these aneurysms often depends on the size and location of the aneurysm, patient characteristics, patient and physician preferences, and the risks of the procedures themselves [42].

Hypersensitivity reactions following implantation of metal medical devices have been reported in the setting of orthopedic, gynecologic, thoracic, and cardiac implants. Therefore, it would be expected that the use of neurovascular metal implants might pose a similar risk of hypersensitivity reactions following implantation. However, there is a paucity of information on this subject, and reports of hypersensitivity reactions following neurovascular implantation are rare. Thus, the incidence of these hypersensitivity reactions is unknown.

The metal composition of these neurovascular implants is important to consider when discussing metal hypersensitivity reactions. The aneurysm clips come in various metallic compositions, including Phynox (cobalt-chromium-nickel alloy), Elgiloy (cobalt-chrome alloy), titanium alloy, and pure titanium. The Phynox and Elgiloy aneurysm clips contain common metal allergens that have the potential to induce hypersensitivity reactions. The endovascular coils used to treat cerebral aneurysms include Guglielmi detachable coils, mechanical detachable spirals, and interlocking detachable coils. The Guglielmi detachable coils are the most widely used, but all are composed of platinum alloy. Most of the intracranial stents used consist of nitinol, which is composed of 55% nickel and 45% titanium [6]. Given that these neurovascular implants are composed of metals that are common allergens, there is a possibility of developing postoperative complications associated with metal allergy.

Reports of complications associated with metal hypersensitivity reactions following implantation of various neurovascular implants have been increasing. These reactions have been observed in patients undergoing treatment of ruptured and un-ruptured cerebral aneurysms with both intracranial aneurysm clips and endovascular coils. The reported complications range from mild to severe, debilitating and potentially fatal. Uwatoko et al. [43] reported a case of a patient who underwent endovascular repair of a cerebral aneurysm with platinum coils and developed edema of the eyelids and lips with an associated rash that extended to the neck 1 month after the procedure. Patch testing was performed, which showed positive reactions to platinum, a component of the coil, as well as nickel and chromium. The patient's symptoms gradually resolved following treatment with low dose oral corticosteroids and antihistamines, suggesting that the reaction had been secondary to metal hypersensitivity [43]. Symptoms did not recur following medical treatment, and removal of the coils was not required. Xue et al. [44] reported a case of a young woman who immediately developed transient numbness and tingling of the left face and persistent left sided headache following endovascular coiling of a left supraclinoid carotid ophthalmic artery aneurysm. Three months later, she developed additional paresthesias of her right extremities. An MRI showed enhancing white matter lesions, but an infectious and rheumatologic workup was negative. However, she did have a history of skin irritation to certain jewelry. The patient was treated with 2 weeks of systemic steroids, and her symptoms completely resolved. Patch testing performed 1 year after the procedure revealed positive reactions to nickel and sodium tetrachloropalladate (II) hydrate. The endovascular coils used to occlude the patient's aneurysm were stainless steel, composed of chromium, nickel, and molybdenum alloy [44]. Therefore, the temporal pattern, the patch testing results, and the resolution of the patient's symptoms with systemic steroids suggested that the symptoms were secondary to a metal hypersensitivity reaction. Ross et al. [45] reported a case of a patient who developed a generalized pruritic papular eruption 1 month following surgical clipping of a ruptured aneurysm with a Phynox aneurysm clip. Replacement of the clip with a titanium clip led to the resolution of the patient's symptoms, and histopathological specimens obtained during removal confirmed a delayed type IV hypersensitivity reaction [45]. While these case reports represent mild post-implantation complications possibly associated with metal hypersensitivity, there are other reports of severe

neurological damage following implantation of aneurysm clips or endovascular coils.

Two case reports in the literature describe severe and debilitating neurological complications that occurred following implantation of an aneurysm clip. Schmidlin et al. [46] reported a case of a patient who underwent surgical clipping of a left posterior cerebral artery (PCA) aneurysm with a nickel-containing aneurysm clip and subsequently developed bilateral cerebral infarctions and severe neurologic deficits. The patient had a history of a rash after wearing certain jewelry and was suspected to have a nickel allergy. The patient was given high-dose methylprednisolone, and patch testing demonstrated a weakly positive reaction to nickel. A month after the initial procedure, the nickel-containing aneurysm clips were replaced with titanium clips. The patient's acute symptoms improved, but the patient did not recover neurologic function and was discharged to a long-term care facility, requiring a tracheostomy for ventilation and tube feeding [46]. Similarly, Grande et al. [47] presented a case of seizures, aphasia, and altered mental status following the treatment of an unruptured left PCA aneurysm with a nickel-containing aneurysm clip. Imaging revealed infarctions in the frontal lobes and the PCA distribution. After replacing the nickel aneurysm clip with a clip composed of titanium alloy, the patient recovered enough to be discharged to a long-term care facility [47]. These studies demonstrate the debilitating neurological consequences possibly associated with metal hypersensitivity following insertion of aneurysm clips and endovascular coils for the treatment of ruptured or un-ruptured cerebral aneurysms.

There have also been reports suggesting metal hypersensitivity reactions induced by the use of metal intracranial stents. Ulus et al. [48] reported headaches and visual disturbances associated with lesions in the frontal, parietal, temporal, and occipital lobes and cerebral edema 1 month after stent-assisted coiling to treat an un-ruptured left middle cerebral artery (MCA) aneurysm. A nitinol stent was used with platinum coils, and the authors suggested that the postoperative reaction was secondary to a possible nickel allergy. However, no treatment was given, and the patient's symptoms resolved over 2–3 weeks [48]. Therefore, in the absence of postoperative patch testing and an unknown response to a trial of steroids, it is unclear whether this reaction was associated with metal hypersensitivity. If the reaction was secondary to metal hypersensitivity, it would be hard to discern whether it was due to a nickel or platinum allergy, given that there are previous reports of postoperative hypersensitivity reactions associated with both platinum coils and nickel-containing clips.

While many of these studies lack definitive confirmation that the complications following implantation are secondary to metal hypersensitivity (i.e., patch testing), the resolution of symptoms seen with removal of the clips and the use of immunosuppressant therapy support this argument [17]. In addition, the histopathological specimens obtained and examined in some reports were consistent with a delayed type IV hypersensitivity reaction, further supporting the notion that these complications were secondary to metal hypersensitivity induced by the neurovascular implant.

Currently, there are no consistent standard preoperative methods of testing for metal hypersensitivity prior to neurovascular implantation. This is likely due to the paucity of reported complications associated with metal hypersensitivity following placement of an aneurysm clip or endovascular coiling. The wide spectrum of potential complications associated with metal hypersensitivity following neurovascular implantation and the infrequency of these reactions may make the need for preoperative patch testing difficult to determine. In some cases, patients developed mild reactions that resolved without treatment or with immunosuppressant therapy alone. Removal of the neurovascular implant was not required and the reaction did not recur [43, 44, 48–50]. Xue et al. [44] argued that in the context of a rare, transient reaction that only requires supportive care, preoperative patch testing may

not be necessary as it would not significantly change management. A positive preoperative patch test may not accurately predict a postoperative hypersensitivity reaction, and an implant containing the allergen identified on patch testing may still be used without consequence. However, the increasing reports of debilitating and potentially fatal neurological complications following neurovascular implantation support the use of preoperative patch testing to detect metal allergy prior to implantation to prevent these severe complications. These more severe reactions were not successfully treated with systemic immunosuppressive therapy alone but required removal of or exchange of the implant for a non-allergenic implant (i.e., titanium clip) [45–47]. The patients were subjected to another invasive procedure in order to appropriately treat the postoperative complications associated with metal hypersensitivity. In some cases, removal of the aneurysm clips or coils may be impractical or difficult given the patient's condition and may make finding a solution for the hypersensitivity reaction very challenging. Preoperative patch testing may prevent serious neurological complications and the need for additional procedures by preoperatively identifying the patients with a metal allergy. These patients can then receive a non-allergenic implant, which will decrease the risk of postoperative hypersensitivity reactions.

The accepted practice among dermatologists is to utilize preoperative patch testing for patients with a history of metal hypersensitivity or if there is concern for metal hypersensitivity (i.e., report of intolerance to certain metal jewelry) [51–53]. This practice should be considered for patients undergoing neurovascular device implantation when there is a concern. Preoperative screening would help to detect and confirm patients who have metal allergy, which would help to prevent potential postoperative complications associated with hypersensitivity to the implant, whether mild or severe. However, further evaluation of the use of preoperative patch testing in patients receiving neurovascular implants is necessary to determine the clinical utility given that reactions are rare and some are mild to moderate, requiring only supportive care. Table 23.3 summarizes the published evidence related to hypersensitivity reactions to neurovascular implants.

23.4 Oculoplastic Implants

Metal oculoplastic implants are often made of gold, platinum, or titanium. Gold or platinum eyelid weights are used for correction of lagophthalmos. Titanium is used in the form of screws and meshes for orbital reconstruction and pegs for orbital implants. Implantation of gold eyelid weights has been shown to induce hypersensitivity reactions, and although cases of hypersensitivity to cardiac, dental, and orthopedic devices made of titanium have been documented, this has yet to be reported with the use of titanium implants in oculoplastics and orbital reconstruction.

23.4.1 Gold Weights for Eyelid Loading

Lid loading with gold weights is an established treatment for lagophthalmos secondary to facial nerve palsy. The procedure involves inserting a gold weight into a small pocket between the orbicularis oculi and tarsal plate of the upper eyelid [54]. This technique helps to achieve better eyelid closure and subsequently reduces the risk of exposure keratopathy [55]. Historically, several different metals have been used for this procedure, but gold emerged as the material of choice because of its high density, inertness, and ideal color match through the overlying thin skin of the eyelid [56].

Both dental gold and commercially available gold eyelid weights have been used for lagophthalmos correction. Twenty-four karat gold weights are preferred to minimize tissue reaction [57], as dental gold is usually an alloy of 70% gold, 16% copper, 10% silver, and 2% platinum.

Table 23.3 Neurovascular implants

Study	Reference Number	Patient	Procedure	Postoperative complications	Management and outcome
Grande et al. (2015)	[47]	33 y/o woman	Elective clipping of un-ruptured L PCA aneurysm with nickel-containing clip (Yasargil)	Decreased oral intake, fever, altered mental status, aphasia on post-op day 11 and subsequently developed status epilepticus, intubated and placed in medically induced coma; MRI, CT showed infarction in L frontal lobe, infarctions in PCA distribution, midline shift	Emergent decompressive fronto-temporo-parietal craniectomy with biopsies of dura and frontal cortex (non-specific lymphocyte cuffing with few neutrophils and rare eosinophils) IV hydrocortisone post-craniectomy decreased ICP but patient still experienced seizures with new infarctions on CT Nickel clip replaced with titanium alloy clip, patient recovered and discharged to long-term care facility 6 days later
Grewal et al. (2015)	[50]	65 y/o woman	Endovascular coiling of un-ruptured PCA aneurysm with platinum bioactive cerecyte coils	L sided weakness and enhancing white matter lesions in ipsilateral hemisphere on MRI post-op day 4	Tested positive for cobalt allergy; patch cover skin test with coil negative No reaction after platinum coil, cerecyte coil, and PGLA implanted into forearm for 2.5 weeks Oral steroids and mycophenolate led to resolution of symptoms and imaging findings Symptoms and imaging abnormalities recurred when weaned off immunosuppressant therapy Patient remained on mycophenolate 47 months after procedure and asymptomatic
Ross et al. (1998)	[45]	36 y/o woman	Repair of ruptured MCA aneurysm with Phynox (cobalt alloy) aneurysm clip	Generalized, intense pruritus and papular rash 1 month post-op	Patch testing was strongly positive to nickel and cobalt Oral prednisone failed to control symptoms Replacement of cobalt alloy clip with titanium clip led to complete resolution of symptoms Histopathological specimen taken intraoperatively confirmed delayed hypersensitivity reaction

Schmidlin et al. (2015)	[46]	33 y/o woman with history of metal hypersensitivity	Elective clipping of un-ruptured L PCA aneurysm with nickel-containing fenestrated aneurysm clip	Altered mental status, aphasia, fever with neurologic decline, and status epilepticus post op day 10; MRI demonstrated bilateral cerebral infarctions with midline shift and downward herniation post-op day 17; complete occlusion of L PCA based on cerebral angiography post-op day 27	Decompressive L frontotemporal craniectomy with cortical biopsies (scattered eosinophils with perivascular lymphocyte cuffing, more inflammation than expected with cerebral infarction) (POD 17) High-dose IV methylprednisolone followed by oral prednisone (started POD19) did not resolve inflammation or vessel occlusion Patch testing was weakly positive to nickel (POD 30) Nickel-containing clip replaced with titanium clip (POD32) Patient did not recover neurologic function but recovered enough to be discharged to long-term care facility requiring tracheostomy, mechanical ventilation, and feeding tube
Tan et al. (2014)	[49]	60 y/o female with history of nickel allergy	Elective repair of R MCA aneurysm with Phynox aneurysm clip	New-onset headaches of increasing intensity and relapsing, remitting cerebral edema demonstrated on MRI 4 years postoperatively	Exploratory stereotactic craniotomy demonstrated gross edema and inflammation; unable to exchange Phynox clip for titanium clip due to significant scarring Histopathology consistent with cell-mediated hypersensitivity reaction Oral prednisolone post-craniotomy resolved symptoms and cerebral edema on MRI at 4 months
Ulus et al. (2012)	[48]	41 y/o woman	Stent-assisted coil embolization of un-ruptured saccular L MCA aneurysm using two nitinol stents and platinum coils	Headache and visual disturbance 1 month post-op; MRI showed multiple lesions in L frontal, parietal, temporal, occipital lobe with edema 1 month post-op	No treatment given Patient's symptoms gradually resolved over next 2–3 weeks, and MRI showed resolution of changes
Xue et al. (2016)	[44]	39 y/o woman with history of skin irritation to jewelry	Endovascular coiling of L supraclinoid carotid ophthalmic artery aneurysm with stainless steel coils (nickel, chromium, molybdenum)	Immediately developed transient numbness and tingling of L face and persistent L sided headache; 3 months later developed additional paresthesias of R extremities and enhancing white matter lesions on MRI	2 weeks of systemic steroids led to resolution of symptoms Patch testing 1 year post-op was positive to nickel and sodium tetrachloropalladate (II) hydrate

The composition of gold alloys influences the rate of gold's dissolution, and alloys with higher copper content result in more gold being dissolved and increased rates of reactivity [58].

Traditionally, gold allergy was thought to be relatively rare due to the inert nature of metallic gold, but in 1994 Bjorkner and colleagues published the first series of screening patch testing to include gold. The data showed that 8.6% of the 823 subjects had positive reactions to gold [59]. A similar frequency was seen when Fowler et al. published data on gold allergy from the North American Contact Dermatitis Group demonstrating 9.5% of 4101 subjects patch tested had a positive reaction to gold [60]. In order for gold to become allergenic, some ionization must occur. This may transpire in the setting of small amounts of sweat coming into contact with gold jewelry, ingestion of gold-containing medications, or installation of dental gold [61, 62].

Gold eyelid weights have been used for over 50 years with relatively few case reports of complications attributed to gold allergy, although the frequency of contact allergy to gold weights has not been systematically studied [54, 56]. Bjorkner describes four cases of women who underwent lid loading surgery with gold weights for lagophthalmos and subsequently developed symptoms of swelling and erythema of the eyelid that resolved after the gold weight was removed. All four of these patients also tested positive to patch test preparations using 2% gold sodium thiosulfate (GST) in petrolatum [54]. Doyle et al. [55] reported two cases of patients who developed eyelid dermatitis shortly after lid weight implantation. One of the patients was patch tested and found to have a positive reaction to 2% GST. Although the other patient refused patch testing, histological evaluation of the fibrous capsule obtained during surgical removal of her gold weight was suggestive of a delayed type hypersensitivity reaction. Both patients experienced resolution of their symptoms after removal of the gold weights [55]. These cases exhibiting a pattern of new cutaneous eyelid symptoms beginning shortly after gold was implanted into the eyelid, accompanied by positive patch testing or histological evidence supporting type IV hypersensitivity reaction, and subsequent improvement in symptoms upon the weight's removal, argue for the presence of a post-implantation hypersensitivity reaction.

Patch testing with gold sodium thiosulfate has a relatively low specificity (a positive patch test to GST is usually not accompanied by intolerance to gold jewelry). Ahnlide et al. [63] demonstrated that only 40% of patients with positive patch tests to gold may develop contact dermatitis when exposed to metallic gold. Although this is a relatively low positive predictive value, cutaneous exposure to gold may be a less potent inducer of allergy than subcutaneously implanted gold such as gold lid weights. Not only is implanted gold a more chronic form of exposure but it is expected that a larger amount of ionization would occur [64]. Furthermore, the skin of the eyelids is particularly susceptible to allergic reactions, and it has been shown that gold allergy in general has a propensity to cause facial and eyelid dermatitis [61]. Doyle and colleagues proposed patch testing be performed if there is a positive family history of gold allergy, if there is a questionable personal allergic reaction that could be attributed to gold, or in patients who have previously undergone dental restoration involving gold and thus may have become sensitized [55]. In patients who endorse a history of gold allergy, or have a positive patch test, implantation with a platinum weight is a suitable alternative. Table 23.4 summarizes the published evidence related to hypersensitivity to oculoplastic implants.

23.5 Nuss Bar

The Nuss bar is a convex, stainless steel bar used for the treatment of patients with pectus excavatum. Pectus excavatum (PE), also known as funnel chest, is a common congenital chest wall deformity resulting in narrowing of the thoracic cavity and a caved-in appearance of the anterior chest wall [65, 66]. It can be apparent at birth but frequently develops during the pubertal growth spurt [66, 67]. Individuals with PE often experience cardiopulmonary symptoms such as chest

Table 23.4 Oculoplastic implants

Study	Reference number	Patient	Preoperative patch testing	Postoperative complications	Management and outcome
Bjorkner et al. (2008)	[54]	Four cases: 1. 51-year-old female with no history of atopy or gold allergy 2. 71-year-old female with history of dental gold for over 50 years 3. 68-year-old female with history of dental gold 4. 77-year-old female with dental gold	None performed	1. Postoperative swelling and erythema, progressively worse over 8 months 2. Postoperative erythema and swelling 3. Erythema and swelling of eyelid and ipsilateral forehead and cheek 1 week after gold eyelid weight was implanted 4. Erythema and swelling of eyelid for years after implantation, with eventual spontaneous extrusion of the eyelid weight	1. Postoperative patch testing positive to GST 2%. Gold weight was replaced with platinum weight and symptoms gradually subsided over 10 months 2. Postoperative patch testing negative. Symptoms resolved when gold weight was replaced with platinum 3. Symptoms resolved over the period of 4 months after gold weight was replaced with platinum weight. Postoperative patch testing showed positive reactions to 2% and 5% GST. Pt also became unable to wear gold jewelry 4. Post-op patch testing to 2% and 0.5% GST were positive. Symptoms improved after weight was removed
Doyle et al. (2005)	[55]	1. 67-year-old female with positive family history of allergy to gold, no personal history despite having dental gold 2. 79-year-old female with no family or personal history of gold allergy, no personal dental gold	None performed	1. 2 weeks after implantation, patient developed eyelid dermatitis 2. Eyelid dermatitis appeared 1 week after implantation	1. Dermatitis was unresponsive to topical and oral antibiotics with brief response to topical steroids. Patch testing with 2% GST was positive. Symptoms subsided after weight was removed 2. No response to topical or oral antibiotics. Topical steroids only provided brief relief. Patient refused patch testing. Gold weight was removed with subsequent resolution of symptoms. Histology of fibrous capsule supported delayed-type hypersensitivity reaction with chronic inflammatory infiltrate with few macrophages and mostly lymphocytes. B cells were detected using CD20 stain. Additional stains showed CD4 and CD8 positivity. Reaction was non-granulomatous

pain, dyspnea, cardiac rhythm abnormalities, recurrent respiratory infections, and decreased stamina. In addition, patients with PE also experience significant psychological symptoms including low self-esteem and depression [67, 68]. PE accounts for 90% of congenital chest wall deformities [69]. The incidence of PE is about 1 in 1000 children, with a male predominance and a male to female ratio of 4:1 [65, 66, 70]. Therefore, PE significantly affects many children and adolescents both physically and psychologically.

The Nuss procedure was introduced by Donald Nuss as a minimally invasive technique to correct the chest wall deformity in patients with PE and is currently the treatment of choice for these patients. The procedure involves placement of the Nuss bar behind the sternum, and the bar is left in place for about 2–4 years to allow for thoracic remodeling [67, 71]. The ideal age for undergoing the procedure is between 8 and 12 years old because the rib cage is still very malleable. The Nuss procedure is considered a relatively safe intervention in PE patients, with significant benefits. The Nuss procedure has been shown to be successful in improving cardiopulmonary function and the psychological state of PE patients [67, 68, 72–77]. As a result, patients experience a better quality of life postoperatively.

While the Nuss procedure is determined to be safe and has resulted in significant improvement in the cardiopulmonary and psychological symptoms experienced by PE patients, postoperative complications due to metal hypersensitivity have been reported, which may diminish the improvements in preoperative symptoms. The incidence of metal allergy among Nuss patients is estimated to be as high as 6.4% [78]. The stainless steel Nuss bar is composed of 17–19% chromium, 13–15% nickel, 2.2–3% molybdenum, and <2% manganese. Therefore, metal allergy among patients undergoing the Nuss procedure is a concern preoperatively given the risk of metal hypersensitivity reactions postoperatively. The complications associated with metal allergy following Nuss bar implantation can range from mild local reactions to more severe reactions. These complications manifest as eczema and erythema of the anterior chest wall, protuberant granulation tissue formation, inflammation and drainage at the incision site, lymphadenopathy, persistent pleural effusion and pericarditis, and impaired wound healing [78–81]. Patients may also experience significant and persistent pain leading to limitations in daily activities [78]. An example of a more severe complication associated with metal allergy following the Nuss procedure was described by Obert et al. [82]. The authors reported a case of a patient with a history of nickel allergy who had undergone the Nuss procedure and postoperatively developed granulation tissue and impaired wound healing at the incision sites. These symptoms resolved after removal of the stainless steel Nuss bar. Eleven years after the procedure, the patient presented for a syncopal episode and was found to have a fibrous band of tissue causing severe right ventricle outflow obstruction. This fibrous tissue was thought to have formed secondary to the inflammatory response that occurred in the immediate postoperative period. This case report demonstrates that postoperative hypersensitivity reactions may be more severe than simply dermatitis at the incision site. It also demonstrates that these reactions may not only cause acute complications immediately following the procedure but can lead to late complications months to years postoperatively. Postoperative metal hypersensitivity reactions are clinically significant and can lead to significant pain, discomfort, stress, and anxiety for the patients and their families. The case reports of hypersensitivity reactions following Nuss Bar implantation are summarized in Table 23.5.

With early identification of metal hypersensitivity as the cause of these postoperative complications, the distress and pain experienced by the patient can be reduced. Symptoms usually completely resolve with treatment (i.e., tapered dose of oral prednisone) or after the stainless steel Nuss bar is removed or replaced with a Nuss bar composed of titanium [81]. Nuss bar removal and replacement requires that the patient undergo an additional painful procedure. If wound complications are severe enough, a period of time between Nuss bar removal and replacement is advised. This can be distressing for the patients because

Table 23.5 Nuss bar

Study	Reference number	Patient(s)	Preoperative patch testing	Postoperative complications	Management and outcome
Aneja et al. (2011)	[79]	4 male teenagers who underwent Nuss procedure with stainless steel Nuss bar	All exhibited negative results with pre-op patch testing with stainless steel disc	Most developed persistent, protuberant granulation tissue at the incisions sites, some with yellow drainage; one developed erythema and edema at the incision sites with associated axillary lymphadenopathy; reactions occurred 3–14 months post-op	Two of the four patients underwent post-op patch testing – one tested positive for nickel, and the other tested negative for metal allergy Symptoms resolved with removal of stainless steel Nuss bar after unsuccessful treatment with antibiotics or prednisone
Obert et al. (2014)	[82]	23 y/o male with history of nickel allergy who had undergone Nuss procedure at age 12	None performed	Aseptic hematoma, granulation tissue, and impaired wound healing at incision site 20 months post Nuss bar placement; syncope secondary to right ventricle outflow obstruction due to fibrous band formation 11 years postoperatively	Removal of stainless steel Nuss bar led to resolution of initial symptoms but a serious delayed sequela occurred
Sesia et al. (2013)	[80]	14 y/o male underwent Nuss procedure with stainless steel Nuss bar	Negative results	Bilateral wound drainage and erythema; blisters at incision sites with surrounding erythematous maculopapular rash	Repeat post-op patch testing was positive to copper sulfate and molybdenum 6-month steroid therapy unsuccessful Removal of Nuss bar led to resolution of symptoms
Sakamoto et al. (2014)	[84]	Two brothers with pectus excavatum 23 y/o male with history of metal allergy underwent Nuss procedure with stainless steel Nuss bar 17 y/o male with history of metal allergy underwent Nuss procedure with titanium Nuss bar	Negative results Negative results to titanium	High fever, chest pain, and bilateral pleural effusion; high fever and culture-negative pleural effusion	Oral steroid therapy resolved symptoms Stainless steel bar replaced with titanium bar and steroids continued until bar removed 2 years later Oral steroid therapy resolved symptoms and were continued until bar removal 2 years later

they see their chests revert to the preoperative state even after undergoing the initial procedure they hoped would be curative.

Given the significant complications that can result secondary to metal hypersensitivity, preoperative management of patients undergoing the Nuss procedure is a topic of interest. Preoperative patch testing for patients with a known metal allergy or history of atopy was originally the accepted practice for patients undergoing the Nuss procedure [78, 81]. However, Shah et al. [78] reported a rise in post-implantation metal hypersensitivity reactions despite preoperatively patch testing those with a history of metal hypersensitivity. The results of the study revealed that patients who did not report a history of hypersensitivity experienced post-implantation hypersensitivity-related complications and were found to be metal allergic upon postoperative patch testing. Therefore, preoperative patch testing for all patients undergoing the Nuss procedure is now recommended to prevent postoperative complications associated with metal allergy [78]. The Nuss bar manufacturer, Biomet Microfixation, offers a metal disc to be purchased separately by the surgeon performing the Nuss procedure for preoperative assessment of metal sensitivity. The metal disc is manufactured to be a sample of the stainless steel Nuss bar so that tolerance to the Nuss bar can be evaluated. However, the metal disc has not been found to be accurate in detecting metal allergy prior to the Nuss procedure and appears to be less sensitive than patch testing in defining metal allergy preoperatively [79, 83]. As a result, patch testing is the method of choice to preoperatively evaluate patients for metal allergy prior to Nuss bar implantation. Figure 23.1 depicts a recent patient who was referred for preoperative testing and his clinical outcome.

Patients found to be allergic to a component of the stainless steel Nuss bar on preoperative patch testing receive a titanium Nuss bar to prevent postoperative complications related to metal hypersensitivity. While this may significantly decrease the rate of postoperative complications associated with metal allergy, there are drawbacks to using titanium Nuss bars. The titanium bars are less malleable than the stainless steel bars and more difficult to modify to fit the patient's thoracic cavity during the procedure. The titanium bars are also more expensive than the stainless steel bars, leading to greater operative and hospital costs [78]. In addition, while titanium allergy is rare, hypersensitivity reactions to titanium Nuss bars have been reported, leading to similar symptoms as would occur with the stainless steel Nuss bar [84]. Therefore, the use of titanium Nuss bars does not eliminate the possibility of postoperative hypersensitivity reactions and comes with its own drawbacks.

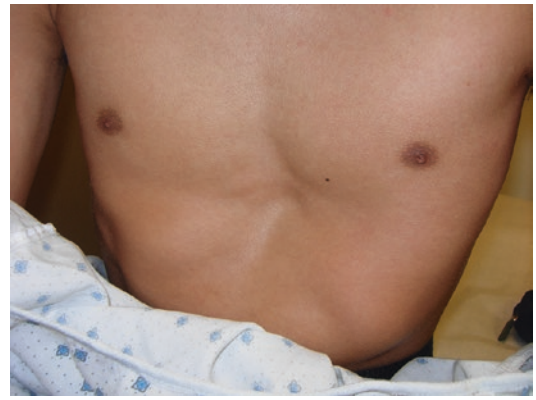

Fig. 23.1 Pectus excavatum of the presternal area of a 14-year-old Hispanic boy who was referred for preoperative evaluation of metal allergy prior to the insertion of a stainless steel Nuss bar. This boy had a history of atopic dermatitis and also had metal orthodontic braces. His patch test to nickel was 1+ at 48 and 72 h, with negative patch tests to cobalt and chromium. Based on these results, his surgeon decided to use a titanium-based Nuss bar, rather than the stainless steel version that was originally planned. He underwent Nuss bar insertion without complications after 2 years of follow-up. This represents an example of how preoperative patch testing affected decision making prior to metal implant insertion, with a favorable outcome for the patient

23.6 Summary

Overall, complications related to gynecologic implants are rare and do not warrant patch testing prior to the insertion of Essure fallopian coils for contraception. Patients with an existing history of nickel allergy have the option of alternate materials prior to the insertion of this coil.

Copper-containing IUDs have been used for many years, and reports of local or systemic allergic reactions to the IUD are very rare. Since copper is a rare cause of metal sensitivity in the general population, predictive patch testing plays no role in decision making related to the use of this type of IUD.

Neurovascular metal implants (clips, coils, and stents) used to treat un-ruptured or ruptured aneurysms are composed of metals (nickel, cobalt, chromates, titanium) that are known to elicit hypersensitivity reactions in the general population. There are rare reports of hypersensitivity reactions to such neurovascular implants, some with devastating outcomes. Management approaches have ranged from operative removal of the implant and replacement with a titanium implant to transient administration of immune suppressive therapies such as oral corticosteroids. Because the role of preoperative evaluations has not been prospectively studied, guidelines are lacking. The general approach would be to preoperatively patch test patients with a history suggestive of metal sensitivity, although the predictive value (tolerance versus hypersensitivity) of this approach is unknown.

The use of metal implants by oculoplastic surgeons is for the treatment of lagophthalmos, and commonly gold weights may be inserted onto the tarsal plate of the eyelid to ensure proper eyelid closure in the setting of cranial nerve palsies. Despite the use of this type of implant for over 50 years, there are only rare cases of clear-cut hypersensitivity reactions to these gold implants (accompanied by positive patch tests to GST), which have been treated by removal with resolution of the patients' symptoms. Predictive patch testing in this setting is indicated only if there is a history of intolerance to gold jewelry or reactions to oral or intramuscular gold therapy or gold-containing dental restorations.

Lastly, individuals with the congenital deformity pectus excavatum are commonly treated with Nuss bar insertion during childhood to surgically correct this defect. Nuss bars are typically composed of stainless steel (a nickel, chromate, molybdenum, manganese alloy). Some of these metals are a common cause of contact hypersensitivity in the general population, and there is good evidence to support preoperative patch testing for all patients undergoing the Nuss procedure to prevent postoperative complications associated with metal allergy. In the setting of pre-existing nickel allergy as demonstrated with a positive patch test, the use of a titanium Nuss bar would be inserted to correct the pectus excavatum, thus preventing complications related to a hypersensitivity reaction to a nickel-containing stainless steel Nuss bar.

23.7 Conclusion

Allergic complications related to the use of implants for gynecologic, neurovascular, and oculoplastic indications are not well studied, and adverse reactions are rare and thus anecdotal in nature. The exception is the Nuss bar insertion for the treatment of pectus excavatum, for which there is enough evidence from limited populations (numerous case series), which suggest that preoperative patch testing may be useful, particularly if there is a history suggestive of an increased risk of metal allergy. In this scenario, predictive testing for metal allergy prior to Nuss bar insertion may prevent the need to remove a stainless steel implant that induces an allergic reaction to nickel, necessitating removal and replacement with a titanium Nuss bar.

Further prospective studies are needed in all of the scenarios to better define the role of predictive patch testing prior to metal-containing implant insertion.

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24 Diagnostic Work-Up of Patients with Metal Implant Failure

Peter Thomas and Burkhard Summer

24.1 The Need for Guidelines for Evaluation of Implant Failure

Considering the annually growing numbers of inserted metal implants, an increasing rate of patients with implant failure might be expected. In Germany alone in the year 2011, 232,320 total hip and 168,486 total knee arthroplasties were performed—and about 10.4% and 9.5% of these, respectively, were complication-related revision surgery. In the USA, the corresponding numbers were 465,034 total hip and 702,415 total knee arthroplasties (10.7% and 8.4% requiring revision surgery, respectively) [1]. The evaluation of failure mechanisms should include implant, surgical, and patient factors. The recent article of Liow et al. [2] about "symptomatic" metal-on-metal (MoM) hip arthroplasty demonstrates in an exemplary manner how the systematic clinical evaluation and management of respective patients can be planned. The diagnostic evaluation includes an arthroplasty-specific history, physical examination, assessment of serum inflammatory markers like CRP, hip joint aspiration to exclude infection (cellular count, leukocyte esterase and alpha-defensin level, PCR), histopathology of biopsy specimen, and radiological studies including standard and metal artifact reduction MRI. Assessment of metal ion level may be used as a surrogate marker of wear, but does not necessarily correlate with clinical and peri-implant tissue reactions. With regard to allergy diagnostics, the authors note that "dermal metal hypersensitivity testing is still controversial, with no evidence based on the most appropriate test for arthroprosthetic metal hypersensitivity." In terms of implant factors, the authors specify that wear and metal ion release depend, for example, on (1) femoral head size and head-neck taper corrosion; or on (2) further component aspects like acetabular cup design leading to head-cup mismatch, disturbed lubrication, and edge loading. A major surgical factor is malpositioning: in the case of MoM, in particular, altered acetabular cup inclination leading to increased wear. Patient factors associated with increased MoM failure rates include, as indicated by Liow et al., female gender, low body mass index (likely because this equals a more active patient), activity level, and metal hypersensitivity. There is another recent example of a proposed set of standardized criteria for the diagnosis, classification, and grading of a metal implant-associated clinical problem [3]: the international consensus on definition, classification, and management of fibrosis of the knee joint.

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This includes diagnostic and management algorithms.

Hypersensitivity reactions may be observed to metallic components of various implanted medical devices and, although uncommon, need to be addressed with appropriate diagnostic tools. Despite the lack of either consensus on the appropriate diagnostic steps or a generally accepted algorithm, we will present current strategies for diagnostic work-up in patients with suspected metal implant allergy.

24.2 Diagnostic Steps: General Considerations

Various restrictions apply to the selection of appropriate steps to evaluate potential implant allergy: (1) apart from cutaneous reactions suggestive of hypersensitivity, many symptoms (i.e., swelling, effusion, pain, aseptic loosening) are nonspecific and hamper the definition of "implant allergy"; (2) proof of a correct diagnosis is often only possible if symptoms resolve upon either implant removal or substitution with a "hypoallergenic" alternative; (3) it has to be clarified whether it is necessary to perform requested allergy diagnostics prior to first implantation or only in the case of a symptomatic implant.

Cutaneous metal allergy (such as eczema) usually presents as a T-lymphocyte-mediated type IV (i.e., delayed-type hypersensitivity, DTH) reaction. As this mechanism is assumed to be predominant in metal implant allergy, several recent publications critically discuss the role of patch testing, lymphocyte transformation testing (LTT), and histopathology [4–13] as diagnostic steps for its verification. Accordingly, peri-implant reactions were described as lymphocyte dominant with prevalent local [14] and systemic TH1-type cytokine expression [15]. In general, patch testing is the gold standard to detect metal allergy if performed by experienced dermatologists or allergologists. The LTT remains a complementary method under the restrictions listed below. Finally, histopathology helps to differentiate the various patterns of peri-implant inflammation (i.e., infectious, foreign body-like, "lymphocyte dominant").

Granchi et al. [16] analyzed 22 publications regarding metal hypersensitivity testing in patients undergoing joint replacement. They stated that patients with failed implants were more likely to have metal allergy but that a causal relationship was difficult to prove. This observation is in accordance with the publication of Amini et al. [12] and with the recent study of Munch et al. [17], in which the authors tried to evaluate the link between metal allergy and symptomatic arthroplasty by matching the arthroplasty and patch test registry data. They could not prove that a positive metal patch test reaction was inevitably linked with complications and revision surgery. According to their opinion, it rather occasionally contributes to implant failure. However, they also stated that, "in cases with multiple revisions, cobalt and chromium allergies appear to be more frequent." Schalock and Thyssen with colleagues [7] published a diagnostic algorithm for the evaluation of suspected metal allergy, suggesting a baseline patch test series supplemented by additional test series according to the respective implant materials. Regarding pre-implant testing, they stated that those patients "with a reported history of metal dermatitis should be evaluated by patch testing." For implant-bearing symptomatic patients, as a minimum requirement, they propose an extended baseline screening and metal screening series. Additional test series are provided in the algorithm.

Patients with cutaneous metal allergy often do not develop complications to implants containing the respective metals. This may be seen at a single patient level [18] or in patient groups such as the 18 metal-allergic patients in whom Carlsson and Möller [19] observed no complications upon arthroplasty with implants containing such metal. When comparing patch test results in 100 symptom-free and 200 symptomatic arthroplasty patients, Thomas et al. found that, even among the individuals free of complaints, 6.4% were allergic to nickel and 6.4% to cobalt [20].

Though there are no uniform consensus recommendations, there are the following assertions:

in 2008, the joint statement of the German Implant Allergy Working Group (AK 20) of the German Association of Orthopedics and Orthopedic Surgery (DGOOC), German Contact Dermatitis Research Group (DKG), and German Society for Allergology and Clinical Immunology (DGAKI) recommended that (1) (only) patients with a reported history of metal adverse reaction should undergo pre-implant patch testing and (2) the patient be clearly informed of allergy risk, and—if the surgeon would prefer the implant with metal constituents the patient is allergic to—consent should be obtained before implanting the potentially allergenic device [21]. In 2008, Geier et al. also published a position paper of the DKG recommending the careful use of the few available evaluated patch test preparations in suspected implant intolerance [22]. In 2011, Thyssen et al. [8] also refuted preemptive testing, but recommended an allergological work-up despite the "difficult debate on allergy work-up of such patients." In 2016, the American Contact Dermatitis Society advised against preventive patch testing, but recommended preoperative testing in patients with a clear history of metal dermatitis and discussed management recommendations, including medicolegal aspects [10].

24.3 Testing Modalities

With regard to testing, two scenarios are possible: testing a patient prior to implantation and testing the patient with the symptomatic implant.

24.3.1 Pre-implant Testing: Routine or Only History-Driven?

Potential future implant components include among others alloying metals and, in the case of arthroplasty, acrylate-based bone cement. Preoperative allergy diagnostics should only be considered in patients self-reporting a history of dermatitis from metal or acrylate contact. In such cases, patch testing to metals (namely, nickel, cobalt, and chromium) or to acrylates and additives (i.e., because of dermatitis to acrylate-based artificial finger nails or dentures) should be performed [8, 10, 22]. On the other hand, patients may well confuse irritative dermatitis, atopic eczema, and much else with "nickel allergy." Correspondingly, Josefson et al. [23] found that a self-reported "nickel allergy" could be verified only in 40% of 369 individuals. At the very least, patch testing will provide clear information regarding the presence of metal sensitization to surgeons. It should be emphasized again that general "preventive" biocompatibility testing is not recommended and that the patch test is not able to predict the development of allergic contact dermatitis or implant complications in yet unexposed individuals [8, 10, 22, 24]. Further, the use of metal discs for biocompatibility assessment [10, 25, 26] is not recommended. Finally, metal LTT is regarded as a potential supplementary method to the patch test, which is considered the gold standard.

24.3.2 Allergy Diagnostics in Patients with a Symptomatic Implant

After exclusion of differential diagnoses such as infection by the referring physician (but also by the dermatologist with regard to the skin eruption), the following diagnostic steps can be taken: patch testing, histological evaluation, and LTT. Figure 24.1 gives an overview.

24.3.2.1 Patch Testing

Patch testing is the gold standard for the in vivo evaluation of DTH. Despite the lack of consensus recommendations, most experts recommend that, at a minimum, a standard patch test series with the major alloying metals nickel, chromium, and cobalt should be performed. A listing of the alloys most commonly used in medical implants and their compositions is provided in Table 24.1. With regard to bone cement components, the testing panel used by the authors includes gentamicin sulfate, benzoyl peroxide, hydroquinone, 2-hydroxyethylmethacrylate, copper-(II)-sulfate, methyl methacrylate, and N,

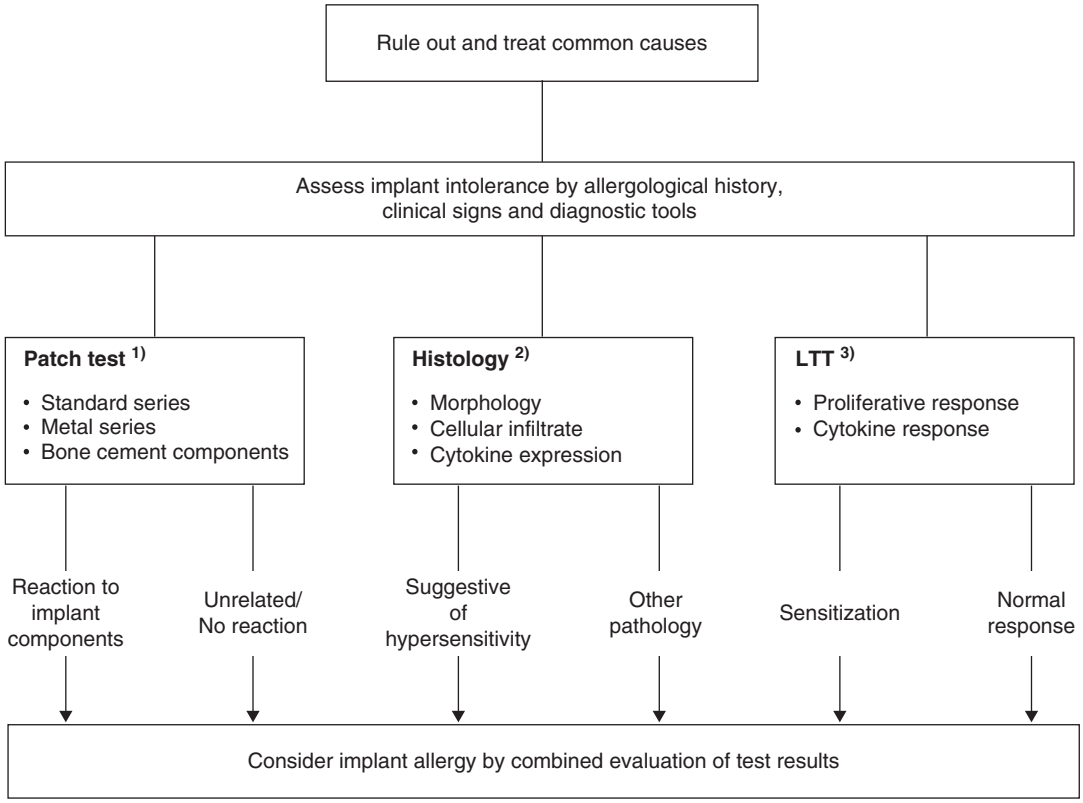

Fig. 24.1 Diagnostic algorithm for patients with metal implant failure and suspected implant allergy. [1)]Late reading (day 6 or day 7) is recommended; testing with metal discs is not recommended. [2)]Distinctive cytokine patterns are still to be defined. [3)]Scientific assay that needs careful evaluation and interpretation; typical allergy cytokine profiles under investigation

N-dimethyl-p-toluidine. Other potential testing series are provided in Chapter 19. A late reading at day 6 or 7 is strongly recommended, since the yield of positive reactions is increased [27–29]. We recently reported 250 symptomatic arthroplasty patients, in whom a late reading resulted in 34% more cases of nickel allergy and even 68% more cases of gentamicin allergy [30]. In our view, gentamicin could be an emerging allergen: we found a substantial 10% sensitization rate within symptomatic arthroplasty patients with gentamicin-loaded bone cement [30]; it is locally released for a long period of time from gentamicin-containing bone cement [31, 32]; and the large majority of patients allergic to it did have symptomatic relief upon revision with gentamicin-free bone cement (paper in preparation). Additional metal preparations are available—but most have not been evaluated and validated. Thus, their use should be decided on a case-by-case basis.

Several authors have stated that patch testing, although valuable in cutaneous contact allergy, cannot prove a causal relationship between implant failure and a dermal reaction [7, 9, 16]. Thus, the significance of test results must be evaluated in the

Table 24.1 Metals/elements in selected alloys that are used in medical implants; variations in content exist, and the distribution listed is considered to be typical for each alloy (Reproduced with permission from [7])

Implant alloy	Alloy elements	Approximate percentage	Use
Stainless steel SAE 316 L	Iron Nickel Chromium Manganese Molybdenum Nitrogen Carbon Sulfur Silicon Phosphorus	Balance 8.3–35 20 2 2–3 0.1 0.03 0.03 0.75 0.045	Cardiac/intravascular devices Orthopedic prostheses, plates, pins, nails, bolts, screws, and fixators Surgical clips/staples
Cobalt-chromium-molybdenum steel	Cobalt Chromium Molybdenum Nickel Iron Carbon Silicon Manganese Tungsten Phosphorus Sulfur Nitrogen Aluminum Titanium Boron	Balance 27–30 5–7 <0.5 <0.75 <0.35 <1 <1 <0.2 <0.02 <0.01 <0.25 <0.1 <0.1 <0.01	Cardiac/intravascular devices Orthopedic prostheses, plates, pins, nails, bolts, screws, and fixators Dental implants and restorations
Vitallium™	Cobalt Chromium Silicon Manganese Carbon Boron Molybdenum Iron	61 32 0.5 0.5 0.02 0.1 5.6 None	Orthopedic prostheses, plates, pins, nails, bolts, screws, and fixators
Titanium alloy	Titanium Aluminum Vanadium Nickel	89.9 5.5–6.5 3.5–4.5 ~0.012–0.034	Orthopedic prostheses, plates, pins, nails, bolts, screws, and fixators Pacemaker shells Surgical clips/staples
Titanium-tantalum-niobium	Titanium Niobium Tantalum Zirconium	53 25 7 5	Orthopedic devices
Nitinol	Titanium Nickel	55 45	Cardiac/intravascular devices Patent foramen ovale and septal defect devices and implants Bone anchors and staples Essure® contraceptive device Urological devices Orthodontics
Oxinium™	Zirconium (oxidized) Niobium	97.5 2.5	Orthopedic joint prostheses

context of additional testing tools or clinical information. Two examples are as follows:

a. The restenosis of gold-plated stents in gold-allergic patients [33]. The diagnosis of "metal implant allergy" resulted from the synopsis of the following findings: patient with disease unexplained by other reasons, contact allergy to implant component, clinical symptoms in the area of exposure, and disappearance of symptoms upon removal of the implant.
b. A patient with dermatitis around a titanium-based pacemaker. The diagnosis of "metal implant allergy" was made because infection was ruled out and histology showed a lympho-histiocytic and eosinophilic infiltrate; LTT showed nickel sensitization; eluate of the "titanium" pacemaker and electrode showed nickel release (correspondingly a stainless steel adaptor for electrode connection was identified as a source of nickel liberation); and the patient became symptom-free upon use of an alternative "titanium" pacemaker [34].

24.3.2.2 Histology

A biopsy should be performed to characterize implant-associated skin reactions. These include eczema, reticular telangiectatic erythema, erysipelas-like reaction, and reactive angioendotheliomatosis [35–38]. With regard to "internal" complications, local infection, foreign body-like, or "hypersensitivity" response to the implant or other unknown peri-implant pathology also has to be evaluated by histology. With regard to artificial joints, the particle size and composition may also lead to different pathologic findings [39].

Histology may be helpful and is one of the diagnostic steps described in the recent international consensus conference on periprosthetic joint infection (PJI) [44, 45]. There is a consensus histopathological classification of the reaction pattern in arthroplasty-related periprosthetic membranes [40, 41]. The initial version of this classification gives four patterns: the particle-dependent foreign body-like response (type I), the granulocyte-dominated infectious type (type II), the combination of types I and II (combined type, type III), and the predominantly fibrotic reaction (type IV, indifferent type). Figure 24.2 shows the four different types [42]. To differentiate between a septic and aseptic peri-implant inflammation, threshold levels for neutrophilic infiltrate (23 neutrophils/10 high-power fields) were postulated and used as indication of infection if exceeded [43]. Willert et al. coined the term "ALVAL" (acute lymphocytic vasculitis associated lesion) to describe a "hypersensitivity-like" lymphocyte-dominated peri-implant inflammation in failed MoM hip arthroplasty [46].

The still missing definition of metal-induced peri-implant allergic reaction might be developed based on the growing number of publications on peri-implant lymphocytic inflammation [46–49]. The role of metal allergy in hip arthroplasty loosening and osteolysis—as assessed by tissue analysis—is discussed in the article of Gallo et al. [49]. Research is ongoing, focusing on functional characteristics of peri-implant lymphocytic infiltration as a further diagnostic tool, for example, with regard to the local cytokine expression pattern [50].

24.3.2.3 Lymphocyte Transformation Test (LTT)

The LTT is an in vitro test that measures the antigen-induced proliferative response of lymphocytes from a patient's blood in the absence or presence of the potential allergen. To determine metal sensitivity, the antigen-induced proliferation is compared in relation to the baseline proliferation of unstimulated cultures and given as a stimulation index [SI]. Details are described in Chapter 12. We and other laboratory groups set the limit for sensitization on SI > 3 [51] and give interpretation only in conjunction with other diagnostic parameters. In Hallab's group—to our knowledge—the threshold is set to a lower limit (SI > 2) [52]. Additional methodological differences may also contribute to interlaboratory variation. Only with the caveat of critical evaluation can the LTT be used as a complementary method, for example, when investigating a suspected allergic drug reaction [53]. However, even for nickel allergy, quality assessments of LTT procedures are very rare [54–56]. Accordingly, the German

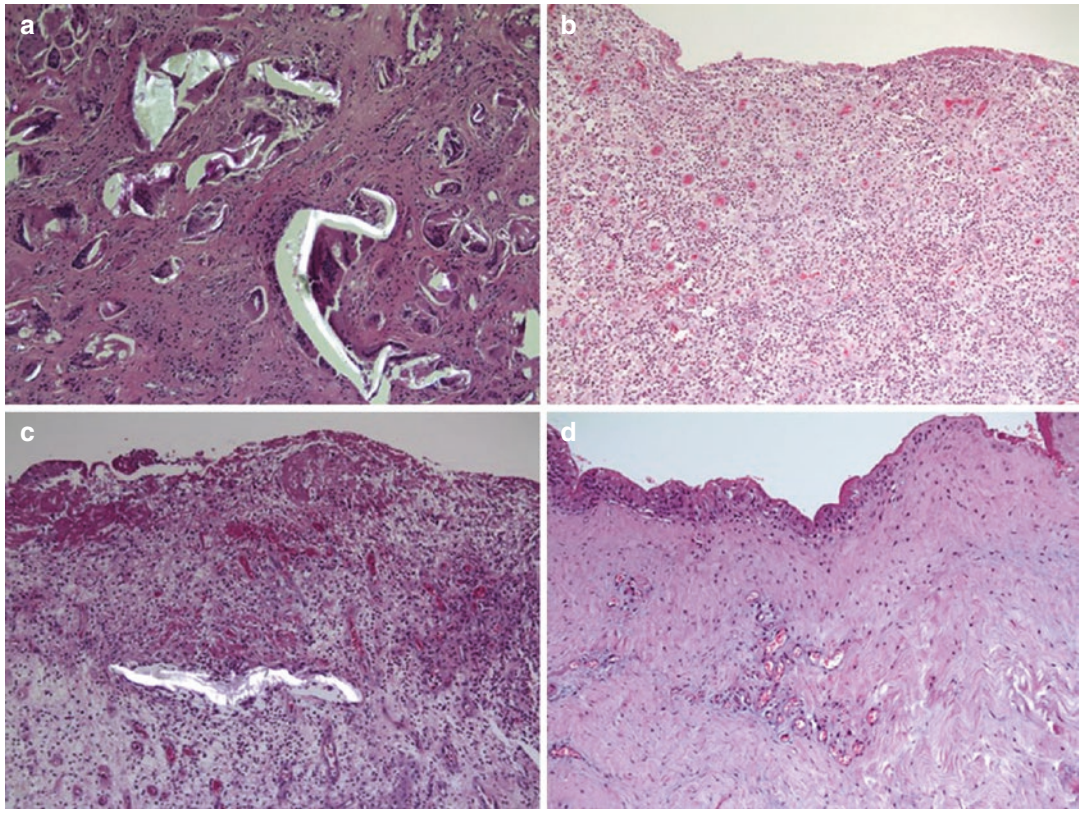

Fig. 24.2 (**a**–**d**) Reaction patterns of periprosthetic tissue. (**a**) Particle-dominated foreign body-like response (type I), (**b**) granulocyte-dominated infectious type (type II), (**c**) combination of types I and II (combined type, type III), and (**d**) the predominantly fibrotic reaction (type IV, indifferent type). (Reproduced with permission from [42])

public authority Robert Koch Institute (RKI) [57], as well as the Canadian Agency for Drugs and Technologies in Health (CADTH) [58], did not recommend the LTT in general. Furthermore, this test remains impractical for routine clinical use, i.e., it is mostly restricted to university laboratory settings. Nevertheless, it is a useful step to prove metal sensitization when the sensitivity and specificity of LTT are evaluated in an experienced laboratory. The best approach would be to integrate its results in a "multistep" diagnostic approach [6, 59].

24.3.2.4 Other Screening Options

Will subcutaneous preoperative embedding of implant alloy discs prove future implant compatibility? No, because no established guidelines exist and sensitization to metal implants may also occur after prolonged latency. Beecker et al. described a patient in whom subcutaneous implantation of metal implant components was done [60]. Due to an asymptomatic course, a corresponding knee arthroplasty was performed, but periprosthetic hypersensitivity reactions developed. Of note, the use of metal discs for patch testing is also not recommended, since this method has not been well evaluated—and even in the case of positive reactions to the disc, the eliciting metal remains unknown [10, 25].

On the other hand, a helpful supplemental diagnostic aid is the assessment of the type and amount of metal release from the "culprit" implant. Thus, proven metal allergy may be linked to actual exposure to the respective metal being released from the device [61, 62]. Finally, we do not recommend the in vitro IL-1ß release assay, which uses peripheral blood samples to evaluate for response to titanium particles, as a predictive test for future "titanium intolerance."

24.4 Outlook

With aging populations, the use of metal implants is continuously increasing. Thus, the understanding and diagnostics of implant failure mechanisms have received growing attention. The accurate diagnosis and stratification of patients with implant intolerance reactions is a major interdisciplinary challenge. Certainly, medical awareness of this condition may vary between different countries. While North American orthopedic surgeons are rather reserved regarding allergy testing, in several European countries, there has been growing attention to this topic—and dermatoallergologists are increasingly receiving consultation requests for the diagnosis of suspected metal implant allergy [63, 64]. The different attitudes are also reflected by the fact that European legislation has long since implemented the Nickel Directive, while in North America, such regulation does not exist. Therefore, an interdisciplinary effort has to be made to increase current knowledge regarding implant intolerance and metal implant allergy.

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Part V

Allergens

Metal Allergy: Aluminium

25

Monica Hindsén

25.1 Introduction

Aluminium is one of the most abundant metals in the earth's crust, and aluminium compounds are widely used [1]. Historically, aluminium was considered more rare and precious than gold and silver. Refining aluminium from ore was a difficult process. The pure form of the metal was first extracted from ore in 1825 by Danish chemist Hans Oersted. Various aluminium compounds are in use: for example, aluminium acetate as an astringent in solutions, aluminium chloride and aluminium chlorohydrate as antiperspirants, aluminium phosphate in cosmetics and dental cement and aluminium hydroxide in antacids. Aluminium-precipitated vaccines and allergen vaccines are commonly used today.

25.2 Aluminium Sensitization and Allergy

Aluminium is considered to be a weak allergen, but contact allergy to aluminium has been more frequently reported in recent years [2]. The most important routes of sensitization to aluminium are aluminium-containing vaccines, hyposensitization with aluminium-adsorbed extracts and contact with aluminium in antiperspirants and other skin products.

Contact allergy to aluminium has traditionally been established by patch testing with aluminium chloride hexahydrate 2% in petrolatum and an empty Finn Chamber made of aluminium. Recently, patch testing with aluminium chloride 10% in petrolatum has been recommended when patch testing a patient strongly suspected of having contact allergy to aluminium [3].

The first report of a patient known to be contact allergic to aluminium is from 1980 [4]. The patient was having hyposensitization therapy to hay fever with an aluminium precipitated allergen. The patient had a positive reaction to the aluminium discs used for testing, and 53 controls were patch test negative when tested with the discs. The patient and controls were patch tested with various test preparations such as aluminium sulphate 2% in water, aluminium chloride 2% in water, aluminium subacetate 1% in water and aluminium powder [4]. Finn Chambers with petrolatum and empty dry Finn Chambers were also used [4]. The patient tested positive to all these aluminium allergens while the controls were all negative [4]. Intradermal testing with aluminium hydroxide in 0.5% in sodium chloride was positive in the patient and negative in controls.

A case report of a girl treated with hyposensitization therapy described itchy nodules at the injection sites [5]. Contact allergy to aluminium was of course suspected. She was tested with aluminium chloride hexahydrate 2%, 4% and

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10% in petrolatum, and the reading performed as usual on days 3 and 7. A positive reaction was only seen to 10% aluminium chloride hexahydrate.

Individuals with persistent pruritic nodules following hyposensitizing therapy and contact allergy to aluminium have been described in several cases [4–9]. A statistically significant association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy has been reported [8].

In a study aimed to quantify the development of contact allergy to aluminium during allergen-specific immunotherapy, a total of 205 individuals in three study groups tested negative to aluminium before allergen-specific immunotherapy started [10]. Four tested positive after therapy, and in the control group, four participants tested positive to aluminium. Six out of the eight who tested positive also had atopic dermatitis. Positive test results were found in 5/78 children, and 3/127 adults also had atopic dermatitis therapy. In this study, immunotherapy was not shown to be a risk factor for contact allergy to aluminium. Among those who developed aluminium allergy, children and those with atopic dermatitis were more highly represented.

In the 1990s in Gothenburg, Sweden, 745 of 76,000 children vaccinated with aluminium hydroxide-absorbed pertussis toxoid vaccine developed subcutaneous nodules at the vaccination site. Four hundred ninety-five children with pruritic nodules were patch tested for aluminium, and 376 were positive [11]. Five to nine years later, 241 of those children were retested with aluminium. Contact allergy to aluminium was no longer demonstrated in 186 of the retested 241 children (77%). Had contact allergy to aluminium disappeared [12, 13]? If the intensity of the initial test result was low, the likelihood of having a negative patch test result at the second test was significantly higher.

Interestingly, when comparing two diphtheria-tetanus toxoid vaccines—one with aluminium hydroxide and one with aluminium phosphate—there were no significant differences between the vaccine groups concerning contact allergy to aluminium, which was not detected [12].

In the literature there are a few reports of patients sensitized to aluminium by contact with other aluminium-containing products. Aluminium compounds can be found in everyday life products from pots and pans, storage containers and foil, to foods and beverages, paints, pigments and cigarette filters. Aluminium may be used in antacid, as an astringent, and in buffered aspirin and topical antibacterial treatments [14, 15]. There are reports of contact allergy to aluminium after using aluminium-containing deodorant [16], eardrops [17] and toothpaste [18] (Table 25.1). Sensitization to aluminium has also been described in a patient with a granulomatous reaction in a tattoo [19].

Occupational contact sensitivity to aluminium is very rare [20]. A machine construction plant worker presented with a 2-year history of eczema on both hands and on the right elbow flexure. At work, he had used a compressed air pistol with his right hand to blow filings made from newly milled narrow aluminium threads. He did not wear protective gloves [21].

In one study, 21 patients with known contact allergy to aluminium were retested with aluminium preparations to find the optimal aluminium test preparation. The patients were tested with various aluminium test preparations, including aluminium chloride and aluminium lactate in equimolar concentrations in a range of 20% to 0.2% of aluminium chloride in petrolatum. Unexpectedly, aluminium chloride hexahydrate 10% gave the highest number of positive reactions to aluminium [4].

Table 25.1 Sources of aluminium

Hyposensitization therapy
Vaccines (i.e. pneumococcal, diphtheria-tetanus-acellular pertussis (DTaP), haemophilus influenzae type b (Hib), hepatitis A, hepatitis B, hepatitis A/hepatitis B, DTaP/inactivated polio, DTaP/inactivated polio/Hib, human papillomavirus, Japanese encephalitis, meningococcal B, Td, Tdap)
Aluminium metal
Deodorants
Eardrops
Toothpaste
Tattoo

Individuals with aluminium allergy may have false-negative reactions. Retesting with aluminium should be considered in patients testing negatively to aluminium when there is a strong suspicion of contact allergy to aluminium [5]. In one study, 17 individuals known to be contact allergic to aluminium were patch tested four times with a serial dilution of aluminium salts, which demonstrated variations in test reactivity. Approximately 49% of the patch test reactions to aluminium lactate and 29% of the reactions to aluminium chloride hexahydrate were negative.

25.3 Management Considerations

Aluminium is used as an adjuvant in vaccines and allergen immunotherapy. Many studies have shown an association between persistent pruritic skin reactions after vaccination and contact allergy to aluminium [22]. These patients may be treated with topical steroids and do not have to avoid vaccination [22]. Unfortunately, lack of awareness of this type of vaccination reaction has at times led to unnecessary extensive diagnostic testing, biopsies and in some cases surgical excision [22]. These pruritic granulomas are benign and self-limited and are not cause to refrain from vaccination, when weighed against the risk for a serious infectious disease [23].

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Metal Allergy: Beryllium

26

James S. Taylor, Raed A. Dweik,
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26.1 Introduction

26.1.1 Beryllium Use and Sources of Exposure

Beryllium is a naturally occurring silver-gray element that is extracted from ores and processed into metals, oxides, alloys, and composite materials [1, 2]. Beryllium is one of the lightest metals with an atomic weight of 9.015, and its specific physical and chemical and properties of low density, high melting point, and atmospheric stability make it commercially important in many common industries and jobs (Table 26.1) [3]. Beryllium's favorable mechanical properties, particularly its specific stiffness (Young's modulus/density), make it very useful for aerospace applications in major components of satellites and spacecraft. Its nuclear properties of functioning as a neutron multiplier with low absorption and high scattering make it a reliable candidate for test reactors and for building nuclear devices for defense applications [1]. Beryllium's combination of unique mechanical, physical, or nuclear properties is like no other material. One of its earliest uses was as a window for x-ray tubes, and in current x-ray technology, beryllium is essential for high-resolution diagnostic x-rays [3]. Within the aircraft industry, it is used in guiding systems for spacecraft, aircraft, and missiles and has become the favored metal for both navigational and optical instruments. Thousands of workers are exposed to beryllium worldwide, and sensitization to the metal continues to occur [3].

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26.1.2 Beryllium Disease: History and Classification

Beryllium was discovered before 1800, but its industrial properties of forming strong, lightweight alloys were not recognized until the 1930s, when it was developed throughout Europe and when manufacturers in the USA imported the methods. Beryllium-associated toxicity and diseases are intricately intertwined with Cleveland, Ohio, where research and production of beryllium began in the 1920s and 1930s, and with the Cleveland Clinic, where reports of pulmonary

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Table 26.1 Industries and jobs with potential beryllium exposure[a]

Industry category	Examples of jobs with potential beryllium exposure	Related products possibly containing beryllium (partial listing)
Aerospace	Deburr worker Grinder Holder Janitor Lapper Machinist Welder	Aircraft and spacecraft spare parts Altimeters Braking systems Bushings and bearings for landing gear Electrical insulators Engines Mirrors in space telescopes Missile guidance systems Precision tools Resistor cores Rockets Satellites
Automotive	Abrasive blaster Booth blaster Maintenance MIG welder Painter Prep shop Ring welder Spray painter Welder	Abrasive blasting media made from coal or copper slag Air-bag triggers Anti-lock brake system terminals Electrical insulators in ignition systems Electronic and electrical connectors Formula-1 race car parts Steering wheel connecting springs Valve seats for drag racer engines
Biomedical	Caster Cutter/grinder Dental technician Induction melter Maintenance technician	Dental bridges Foil masks in X-ray lithography Medical laser and scanning electron microscope components Partials and other dental prostheses X-ray tube windows X-ray windows
Mining	Driller Painter	
Primary metal manufacturing	Abrasive cut-off saw operator Bench grinder Beryllium instrument lab technician Engineer Furnace operator Grinder Inspector Lapper Lathe operator Leach operator Optics worker Ore processer Product controller	Beryllium oxide powder and ceramics, beryllium metal, copper-beryllium alloys, aluminum-beryllium metal matrices, beryllium hydroxide, beryllium fluoride

Table 26.1 (continued)

Industry category	Examples of jobs with potential beryllium exposure	Related products possibly containing beryllium (partial listing)
Manufacturing/consumer products	Abrasive blaster Artist Bencher Brazer Ceramics grinder Chemical operator Crane operator Engine tester Finisher Furnace operator General manager Grinder Incinerator operator Lathe operator machinist Machine operator maintenance Melter Miller Operator-alloy painter Plasma cutter Plating Polisher Pourer Sandblaster Saw operator Shredder operator Solderer Tool and die maker Welder	Abrasive blasting media Bearings Bellows Beryl and chrysoberyl gemstones Bicycle frames Cellular telephone components Clock and watch gears and spring Commercial phonograph styluses Computer disc drives Diamond drill bit matrices Electromagnetic shields Fishing rods Golf clubs Injections molds for plastics Jewelry Manmade emerald and gemstones Musical instrument valve springs Nonsparking tools Personal computer components Precision motion control for automation equipment Radio and laser tubes Rotary telephone springs and connectors Welding electrodes, including bertrandite gemstone electrodes
Defense	Nuclear weapons worker Prep shop	Avionics packaging Electrical insulators in power amplifier tubes and radars Heat shields on missiles a space vehicles Mirror support structures Missile guidance systems Nuclear weapon components Submarine hatch springs Tank mirrors
Construction	Abatement tech Abrasive blaster Carpenter Cutter Electrician Insulator Painter blaster Slater Welder Electrician	Abrasive blasting media made from coal or copper slag

(continued)

Table 26.1 (continued)

Industry category	Examples of jobs with potential beryllium exposure	Related products possibly containing beryllium (partial listing)
Energy and electrical	Welder Electrician	Circuit breaker parts Coal slag Electrical contacts, switches and fuse clips Heat exchanger tubes High voltage electrical components Microelectronics Microwave devices Nuclear reactor components Oil field drilling and exploring devices Relays and switches
Transportation and public utilities	Blaster Mechanic Painter	Abrasive blasting media made from coal or copper slag
Miscellaneous	Artist (e.g. sculptor using beryllium alloys) Electron gun operator Sandblaster Welder	Copper-beryllium alloys

Balmes JR, Abraham JL, Dweik RA, Fireman E, Fontenot AP, Maier LA, Muller-Quernheim J, Ostiguy G, Pepper LD, Saltini C, Schuler CR, Takaro TK, Wambach PF/2014/An Official American Thoracic Society Statement: Diagnosis and Management of Beryllium Sensitivity and Chronic Beryllium Disease/Am J Resp Dis/190/e34-59

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and cutaneous beryllium disease in the 1940s and 1950s were among the first in the USA [4–9]. Van Ordstrand and coworkers described the first three cases of acute beryllium pneumonitis as a new occupational disease in the USA [5]. Van Ordstrand was a Cleveland Clinic pulmonologist who collaborated with industrial physicians at Brush Beryllium Co. along with his clinic dermatology colleagues, initially Earl Netherton [8] and later George Curtis [6, 7]; the group subsequently recounted their more detailed occupational experiences, including acute beryllium skin diseases [6–9]. Following the acute pneumonitis cases, chronic pulmonary disease with skin granulomas was reported [7], and soon thereafter purely cutaneous granulomas inflicted by broken light bulbs were reported from several centers [8, 9]. Hardy and Tabershaw [10] proved that "Salem (Massachusetts) sarcoid" was chronic pulmonary berylliosis, and Hardy developed the US Beryllium Case Registry [9, 11].

26.2 Classification

26.2.1 Occupational Disease

Chronic beryllium disease (CBD), which is a cell-mediated granulomatous hypersensitivity, is the most common chronic occupational reaction to beryllium and typically involves the lungs and skin, with isolated reports of granulomas in the liver, kidney, muscle, and lymph nodes [9, 12].

Acute beryllium disease (ABD) with pneumonitis and dermatitis, as initially described [5–7], occurred primarily in ore extraction operations or in chemical reduction processes [13, 14]. Originally thought to be an irritant phenomenon and a disease of the past [3, 9], ABD was described again by Cummings et al. [15] in 2009. They reported two workers with ABD in the late 1970s and early 1980s with onset of "dermatitis" about 10 days after starting work in the furnace areas, suggesting delayed hypersensitivity rather than irritation, which was

also accompanied by mucosal irritation and nasopharyngitis in one case. Beryllium lymphocyte proliferation test (BeLPT) results were positive in both cases and along with the clinical course suggested a shared immunologic mechanism and a continuum between ABD and CBD. The two workers were exposed to lower beryllium concentrations than workers in the 1940s, and both left employment with a diagnosis of CBD years after initial exposure. Differences in solubility of beryllium compounds were thought to explain differences in disease presentation and progression. Solubility facilitates absorption by sweat [6], producing an irritant dermatitis which induces allergic contact dermatitis, through skin barrier disruption and cytokine release by nonimmune dermal cells. Respiratory tract findings occur by an analogous mechanism [15].

26.2.2 Community-Acquired Disease

Between 1948 and 1969, cases of community-acquired beryllium disease (CA-CBD) were reported in individuals living in relatively close proximity (<0.75 miles) to beryllium extraction and processing plants, who had no occupational or para-occupational exposure to beryllium [16]. At the Cleveland Clinic, prior to the use of the lymphocyte proliferation test, patients with putative CA-CBD were patch tested with beryllium. A positive patch test helped to differentiate CA-CBD from sarcoidosis, with which it may be virtually identical from clinical, histologic, and radiological standpoints [7, 9, 12, 14]. Maier et al. [16] reported eight additional cases of CA-CBD in 2008 from Reading, PA, and recommended further screening and surveillance of those with potential beryllium exposure.

26.2.3 Non-occupational Disease

Beryllium-containing dental alloys have also been reported to cause a number of cases of non-occupational gingivitis and rarely occupational hand dermatitis [17–19].

26.3 Beryllium Skin Disease: Initial Reports and Classification

In 1951, Curtis [6] reported 13 patients with occupational contact dermatitis to beryllium, which was based on positive patch test results in all 13 patients. In 1953, he described in conjunction with his pulmonary and occupational medicine colleagues three of the main types of occupationally acquired beryllium skin lesions—acute dermatitis, beryllium ulcers, and cutaneous granulomas—as part of a more comprehensive report of all clinical types of berylliosis observed over a 12-year period [7]. In the acute dermatitis group, there were 146 cases of allergic contact dermatitis and 63 cases of irritant contact dermatitis among a group of 431 patients with occupational or para-occupational exposure to beryllium [7].

Epstein [13] divided beryllium skin disease into five distinct groups dependent on the specific form of beryllium, personal susceptibility, or both. This classification is mostly based on older occupational reports, and formal reports of cases are now infrequent.

26.3.1 Immediate-Onset Skin Diseases [13]

The immediate-onset diseases essentially occur only during ore extraction and chemical reduction processes. The intensity of the skin reaction and time of onset are a function of the solubility of the salt and degree of exposure.

26.3.1.1 Irritant Dermatitis

Caused by prolonged or unusual contact with soluble beryllium salts, these lesions are not unique to beryllium but represent a typical contact dermatitis and are generally confined to exposed surfaces. Lesions are more common after continuous moderate exposure to mists or soluble fumes. The order of irritation of beryllium salts from most irritating to least irritating is fluoride, ammonium fluoride, sulfate, and chloride.

26.3.1.2 Allergic Contact Dermatitis

Allergic contact dermatitis is caused by the same beryllium salts and typically occurs 6–15 days after initial exposure to fumes, mists, and/or dusts of beryllium fluoride (BeF). One to 25% of those exposed were estimated to be affected. Symptoms were often sudden in onset with pruritus and eyelid edema common; persistent disease often resulted in permanent transfer of workers to areas without BeF exposure. Experimental studies in volunteers, however, sensitized 90% of those patch tested with BeF 1%, with less than 1% sensitized with BeF at 0.1% concentration.

26.3.1.3 Chemical Ulcer

This painful lesion results from neglected cutaneous lacerations or abrasions which are contaminated with a crystal of a soluble beryllium salt, typically BeF. Necrosis ensues with the formation of a small ulcer with a sloughing irregular surface and faint discharge. Repeated debridement is important to remove the crystal to ensure complete healing.

26.3.1.4 Ulcerating Granuloma

Resulting from subdermal implant of beryllium sulfate (BeS04), this lesion (Fig. 26.1) is an extension of the chemical ulcer and is caused by a beryllium salt of lower irritation and solubility. It resembles a soft clavus, extends deeply, is well defined, and is cured by total excision which histologically shows a foreign body reaction with central necrosis.

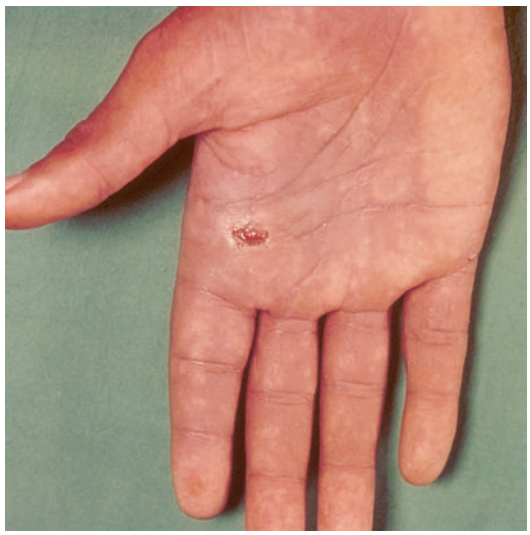

Fig. 26.1 Occupational beryllium chemical ulcer and granuloma of the palm

26.3.2 Delayed-Onset Disease [13]

26.3.2.1 Dermal Granuloma

This lesion historically resulted from breakage of fluorescent light bulbs [8], which have not contained beryllium since the early 1950s [13], or from implantation of beryllium oxide or metal in the workplace and experimentally. The experimental granulomas appeared 4–6 weeks after inoculation of 1% beryllium oxide into the skin [13]. Sneddon [20] described eczematous patch test reactions to a beryllium salt that later became granulomatous, demonstrating for the first time that exposure to certain metals can induce granulomatous hypersensitivity [13].

26.4 Beryllium Skin Disease: More Recent Reports

We [21] recounted the case of a 29-year-old furnace operator in a beryllium production facility who developed lichenoid papules on his forearms (Figs. 26.2 and 26.3) at about the same time that he recorded a positive blood beryllium lymphocyte proliferation test [20]. Skin and transbronchial biopsy specimens revealed granulomatous inflammation. Chest radiograph and computed tomography scan were consistent with beryllium-induced lung disease, and there was deterioration in his pulmonary function tests. Patch testing was not performed. He discontinued working with beryllium and was treated with prednisone 40 mg every other day and high-potency topical corticosteroids.

Most of the remaining reports of contact allergy to beryllium have been from alloys in dental devices and prostheses resulting in gingivitis and stomatitis, and one case of hand dermatitis in a dental technician was also reported [17–19, 22]. In the two cases of Haberman et al. [18], Rexillium III, a beryllium-containing alloy, was identified as

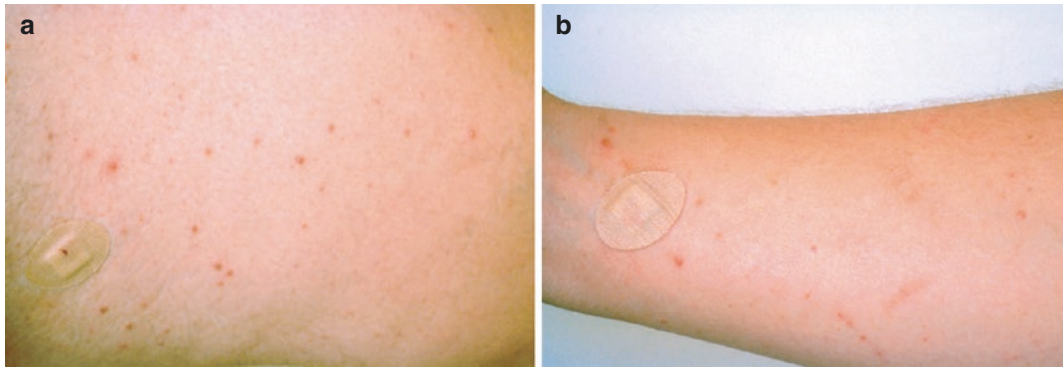

Fig. 26.2 Beryllium granulomas. (**a**) Discrete, lichen planus-like violaceous papules on the forearms, left thigh, and right knee. (**b**) Koebner phenomenon on the right forearm. (Adapted with permission from [21])

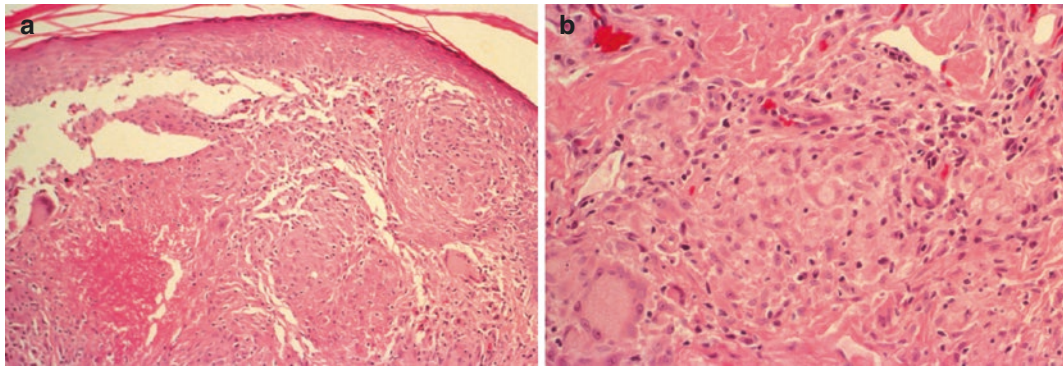

Fig. 26.3 Beryllium granulomas. (**a**) A 4 mm skin punch biopsy shows confluent granulomatous inflammation extending from the dermal-epidermal junction into the reticular dermis. (**b**) Few granulomas demonstrating central fibrinoid necrosis. PAS, GMS, Twort and AFB stains were negative for microorganisms. (Adapted with permission from [21])

the culprit with positive patch tests to the device and to BeSO4; the gingivitis resolved with replacement by non-beryllium-containing alloys.

26.5 Chronic Beryllium Disease (CBD) and Beryllium Sensitization (BeS)

Diagnosis of CBD is based on the presence of (1) a history of beryllium exposure, (2) a positive beryllium lymphocyte proliferation test (BeLPT) either from blood or bronchoalveolar lavage (BAL), and (3) compatible pathology on lung biopsy (usually noncaseating granulomas and/or mononuclear cell infiltrates) [3, 23]. Beryllium sensitization (BeS) is considered to occur with (1) and (2) above in the absence of lung pathology. Determinants of progression from BeS to CBD are uncertain, but higher beryllium exposures and the presence of a genetic variant in the HLA-DP β-chain appear to increase risk [3].

CBD can also be assessed based upon differing combinations of diagnostic criteria including test feasibility and the diagnostic certainty required. These include clinical findings consistent with CBD, history of beryllium exposure, evidence of beryllium sensitization, x-ray findings, lung histology, BAL findings, and pulmonary function test abnormalities [3].

Clinical signs of CBD are nonspecific and include cough, shortness of breath, fever, night

sweats, and fatigue and weight loss. Bronchial symptoms may mimic asthma. Latency is from 3 months to 30 years [23].

According to Newman and Maier's observations and photograph [23], cutaneous nodules on exposed skin surfaces—fingers and forearms—develop if beryllium penetrates the skin and are generally smaller than similar nodules in sarcoidosis, consistent with findings in our case [21]. Digital clubbing may be seen in advanced pulmonary disease [23].

26.6 Beryllium Patch Test

In the first report of 13 cases of allergic contact dermatitis to beryllium [6], patch testing was performed with various unbuffered solutions of beryllium salts (fluoride, sulfate, chloride, and nitrate) with positive test results in concentrations ranging from ~2% to dilutions of ~0.01%. BeF produced the most positive reactions, and patch tests with elemental and powdered beryllium and beryllium discs were negative. Of greater significance were the spontaneous flares in 8 of 16 control patients at 7–16 days. Upon retesting, a number of these controls developed positive patch test reactions at 48 h, consistent with patch test sensitization. In 1959, Curtis [24] reviewed the role of the beryllium patch test in diagnosing 32 cases of CBD. Given the accompanying exposure history and typical chest x-ray findings in these patients, he noted that a lung biopsy was not considered necessary in 25 of the 32 cases. He also reported that 21 control patients with lung disease were patch test negative except for one with a spontaneous flare [24].

In addition to patch test sensitization, Waksman [25], in a commentary of Curtis's article, expressed concern that the beryllium patch test may flare patients with lung disease and "may be dangerous in patients with and without berylliosis or in those patients in remission" [25]. Sneddon [26, 27] reported a temporary flare of lung disease with a positive patch test to beryllium, and there were other such anecdotal reports [26–28].

With the advent of the beryllium lymphocyte proliferation test (BeLPT) after 1970, patch testing with beryllium generally fell into disfavor and is essentially not used in the pulmonary and occupational health arenas. However, with the reports of patch testing used to diagnose contact allergy to beryllium dental alloys, Bobka et al. [29] restudied the beryllium patch test, comparing results with the BeLPT. They reported 11 patients with CBD, 3 with beryllium sensitization without disease, and 20 control subjects with dermatitis and concluded that patch testing may be of value as an adjunct to the BeLPT, clarifying false-negative or ambiguous blood test results. Six of the fifteen subjects with positive patch tests to beryllium had normal BeLPT test results. They found more consistent patch test results with BeSO4 at 1% aqueous concentration versus 1% in petrolatum. Seven of the fifteen had positive or equivocal patch test results at 0.1% aqueous concentration. Skin biopsy specimens taken at different times from the positive patch test sites in five patients displayed typical eczematous reactions initially, with noncaseating granulomas appearing within 18 days. None of their patients had exacerbations of their pulmonary disease, as had been reported elsewhere [26–28]. They did not address the theoretical risk that patch testing could induce sensitization to beryllium in some people and thus increase their risk of developing CBD with further exposure [29]. Likely as a result of this study, a positive patch test to beryllium is now listed as an allowed criterion for BeS [3].

More recent articles note the potential for active sensitization by routine patch testing with beryllium and recommend that it be used only on an "aimed" basis when there is a high probability of exposure [30, 31]. Bircher also noted that analysis of dental alloys for metals could be performed by energy-dispersive x-ray spectroscopy, a noninvasive procedure [31].

26.7 Beryllium Lymphocyte Proliferation Test (BeLPT)

Currently the BeLPT is the cornerstone of both medical surveillance and the diagnosis of BeS and CBD [3]. The BeLPT is considered to identify clinically significant BeS and CBD earlier and better than any other test (i.e., before other tests become abnormal) and to identify BeS and CBD cases which are missed by conventional

screening methods. The BeLPT has both high positive and negative predictive values in screening workplace populations since asymptomatic BeS cases can progress to CBD. Thus, the BeLPT improves diagnostic accuracy and corrects mistaken diagnoses of beryllium disease.

The value of the BeLPT and other recommendations for the diagnosis and management of beryllium disease are detailed in an evidence- and consensus- based 2014 official statement of the American Thoracic Society (ATS) [3]. The BeLPT is considered "abnormal" if two or more of the six stimulation indices exceed the normal range. The diagnosis of BeS in beryllium-exposed workers undergoing medical surveillance may be based on two abnormal BeLPTs, one abnormal and one borderline blood BeLPT, or one abnormal BAL BeLPT. The ATS statement also includes a positive patch test to beryllium as an additional allowed criterion for BeS. Workers with BeS are then entered into a more intensive second-stage testing program for evaluation of potential progression to CBD.

Harber et al. [32] recently analyzed 532 subjects from the Beryllium Biobank (BBB) data from 5 collaborating centers and noted that, cross-sectionally, LPT stimulation index (SI) magnitude was not able to distinguish, among beryllium exposed, BeS or CBD. The likelihood of progression from BeS to CBD was associated with the absolute value of the LPT SI. They noted that prediction of disease progression may be improved by changing the cut point for interpretation or by using the SI as a continuous variable [32].

In a subsequent study utilizing BBB data, Harber and Su [33] reported that the accuracy of identifying BeS is reduced as the number of repeated tests increases and suggested that modification of second-stage screening intervals based on personal risk data would improve cost-effectiveness [33].

26.8 Skin Exposure to Beryllium

Current evidence strongly implicates skin contact with beryllium, specifically soluble salts [6], as causing BeS in humans and poorly soluble beryllium oxide particles [34] as causing beryllium sensitization in mice [35]. Tinkle et al. [34] showed that penetration of beryllium oxide particles was possible ex vivo for the human intact skin at particle sizes of less than or equal to 1 μm in diameter as confirmed by scanning electron microscopy. Surrogate fluorescent particles up to 1 μm in size could penetrate the mouse skin in a model designed to mimic the flexing and stretching of the human skin in motion [34]. Beryllium is also a potent sensitizer in the guinea pig [36] and a grade IV allergen in the human maximization test [37]. In an experiment that likely would no longer be approved, Epstein and Byers demonstrated the first transfer of contact sensitivity (to beryllium) in humans utilizing dialyzable leukocyte extracts (transfer factor) [38]. Additional skin exposure studies are reviewed in the January 2017 OSHA final rule on beryllium [35].

26.9 Management of Beryllium Disease

Periodic evaluation every 1–3 years is recommended by the ATS to monitor if conversion of BeS to CBD has occurred. This includes symptom review, physical examination, and pulmonary function tests followed by a chest computed tomography scan if pulmonary function has deteriorated and bronchoscopy on a case-by-case basis [3].

Corticosteroid therapy is initiated when a patient with CBD exhibits significant lung function decline, utilizing prednisone 20–40 mg daily or every other day for 3–6 months. Corticosteroid-sparing agents (methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and infliximab) are considered with significant side effects [3].

26.10 Prevention of Beryllium Disease

There is a large population at risk of CBD, estimated to include 300,000 persons in the USA [33]. Prevention goals are to limit inhalation and dermal exposure to beryllium as much as possible and to reduce the number of employees who are directly or indirectly exposed. From the most

to least effective, these measures include elimination or substitution, engineering and industrial hygiene controls (isolation of the operation and local exhaust ventilation), personal protective equipment, and administrative changes such as preventing nonessential contact with beryllium.

A critical component of limiting workplace exposure are the US Occupational Safety and Health Administration (OSHA) standards for occupational exposure to beryllium and beryllium compounds. OSHA has just determined that the prior permissible exposure limits (PELs) exposed workers to "significant risk of material impairment to their health," including chronic beryllium disease and lung cancer [35]. A 287-page final rule setting new standards for beryllium was published in the Federal Register on January 9, 2017 [35]. The rule establishes new PELs of 0.2 μg of beryllium per cubic meter of air (0.2 $\mu g/m^3$) as an 8 h time-weighted average and 2.0 $\mu g/m^3$ as a short-term exposure limit determined over a sampling period of 15 min. Other provisions in the final rule designed to protect workers include requirements for exposure assessment, methods for controlling exposure, respiratory protection, personal protective clothing and equipment, housekeeping, medical surveillance, hazard communication, and recordkeeping. Three separate standards were issued for general industry, shipyards, and construction, in order to tailor specific sector requirements. In a recent editorial [39], Borak asserted that BeS does not follow traditional dose relatedness with respect to cumulative and average exposure levels. BeS was said to be associated with (1) short-term peak exposures, which cannot be measured by full-shift personal lapel breathing zone air sampling, and (2) highest job exposures, which cannot be measured by real-time monitoring of personal breathing zone sampling. He proposed that employers and workers should implement more stringent controls on airborne exposures and greater use of skin protection and medical removal for workers with BeS [39].

It is important to understand that the PEL for workroom air levels of beryllium does not protect workers from dermal exposure or from skin sensitization. Skin wipe sample analysis of dental laboratory technicians performing grinding operations demonstrated that beryllium was on the workers' hands even when airborne exposures were well below the time-weighted average PEL [39]. Thus, the recommendations in the final OHSA rule on environmental controls and personal protective equipment are important to implement [35].

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Metal Allergy: Chromium

27

Yolanda S. Hedberg

27.1 Prevalence of Allergy and Epidemiology

Chromium (Cr) has traditionally been the third most common metal allergen (after nickel and cobalt) [1, 2], but ranges from the first to the fifth most common metal allergen in different occupations and countries (Fig. 27.1). Its prevalence varies largely among different groups and countries and over time, closely related to occupations, exposure, different regulations, and work hygiene. Figure 27.1 shows the large variation in the percentage of positive patch test reactions among adults to potassium dichromate (0.25% or 0.5% in petrolatum) found in different studies after the year 2000. Studies on the prevalence of allergic Cr contact dermatitis before the year 2000 have been summarized in [3] and in [4].

Generally, prevalence of allergic Cr contact dermatitis is lower in North America and Western Europe compared with Eastern Europe and Asian countries (Fig. 27.1). This corresponds with a long-term decrease in allergic Cr contact dermatitis in Western Europe and North America, and a stagnant or increasing trend in Asia [4], and is believed mainly to be related to differences in exposure sources, occupations, and regulatory measures. Differences in referral patterns and false positive or false negative readings could be other possible explanations.

Generally, prevalence of allergic Cr contact dermatitis increases with age [4]. Although contact dermatitis to Cr is usually less common in children compared to adults, it remains an important contact allergen [5–8] and, in some studies and countries (e.g., Italy, Switzerland, India), represents one of the most common contact allergens for children [5].

Traditionally, allergic Cr contact dermatitis has been mostly found in men due to the high prevalence in construction workers [4]. This has, however, recently changed in many countries due to regulatory measures to limit the soluble hexavalent Cr (Cr^{VI}) content in cement in some countries, first implemented in Denmark in 1981 [4, 9, 10]. Other important regulations are the recently implemented restriction of Cr^{VI} released from leather [11] and the general attempt by industry and regulators to replace Cr^{VI} in processes and products, e.g., for electronic equipment [12] and chemicals [13].

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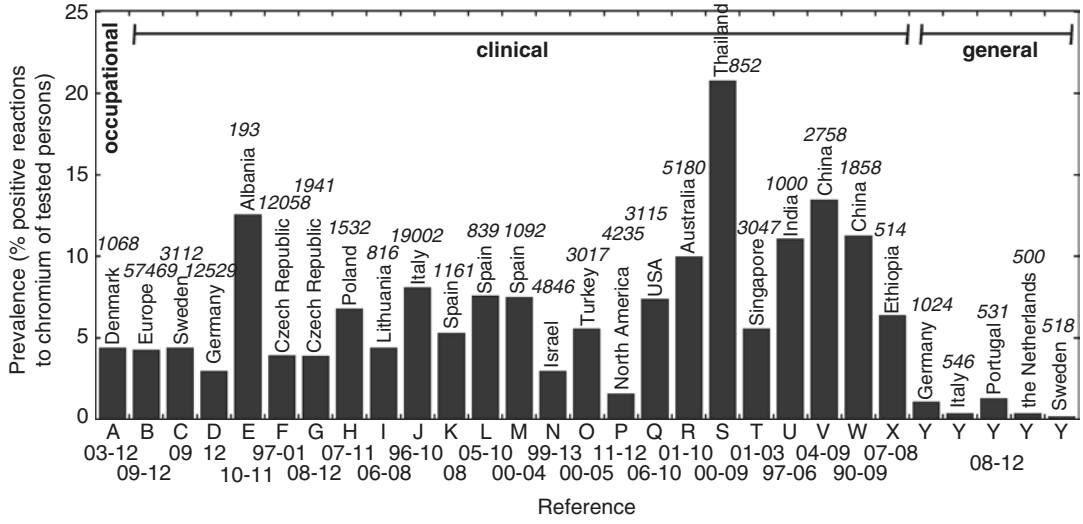

Fig. 27.1 Prevalence of Cr sensitization obtained through patch testing with 0.25% or 0.5% potassium dichromate (in petrolatum) in occupational (blue-collar workers), clinical (e.g., patients suspected to have contact dermatitis), and general population groups in different countries. The study country/region and number of tested persons in each study are noted above the bars, and the years during which the patch testing was conducted (two last numbers of the year only) can be found below the bars and reference letters—A [14], B [2], C [15], D [16], E [17], F [18], G [19], H [20], I [21], J [22], K [23], L [24], M [25], N [26], O [27], P [1], Q [28], R [29], S [30], T [31], U [32], V [33], W [34], X [35], Y [36]. Note that there are differences in patch testing, readings, statistical analysis, etc., among the studies. The reader is referred to the respective study for exact numbers and study details

27.2 Relevant Chromium Chemistry

Trivalent Cr (Cr^{III}) is the hapten that is bound to a carrier (a protein), forming a conjugate (antigen) which causes Cr sensitization and elicitation [37, 38]. Both trivalent and hexavalent Cr species can be stable in aqueous solutions depending on the pH and solution redox potential [39, 40]. Figure 27.2 gives some examples of important trivalent and hexavalent Cr species in aqueous solutions such as patch test solutions. Generally, Cr^{VI} species cannot form cations and do not easily bind to organic species and proteins (unless they are first reduced to Cr^{III}) [41, 42]. This, in addition to their negative charge (at neutral and alkaline pH), has been suggested to be the reason for their relatively high skin penetration [42–44]. Cr^{III}, in contrast, forms a vast number of different cationic, anionic, and neutral charged species in aqueous solutions and binds easily to abundant blood and skin proteins [42, 45–47], but has a low skin penetration and is reported to be rejected by the skin [44].

Metallic Cr, Cr^0, is neither stable in air nor water due to its high oxygen affinity, and it rapidly forms a trivalent Cr oxide. This surface oxide or passive film is important for all corrosion-resistant Cr alloys such as stainless steel, Inconel (a common Ni-Cr alloy), and cobalt-chromium alloys (e.g., used for dental implants and artificial joint prostheses). This surface oxide of noncorroding Cr alloys and metal is very stable. It cannot be seen by the naked eye, because it is very thin (e.g., 2–5 nm in water or air) [48, 49].

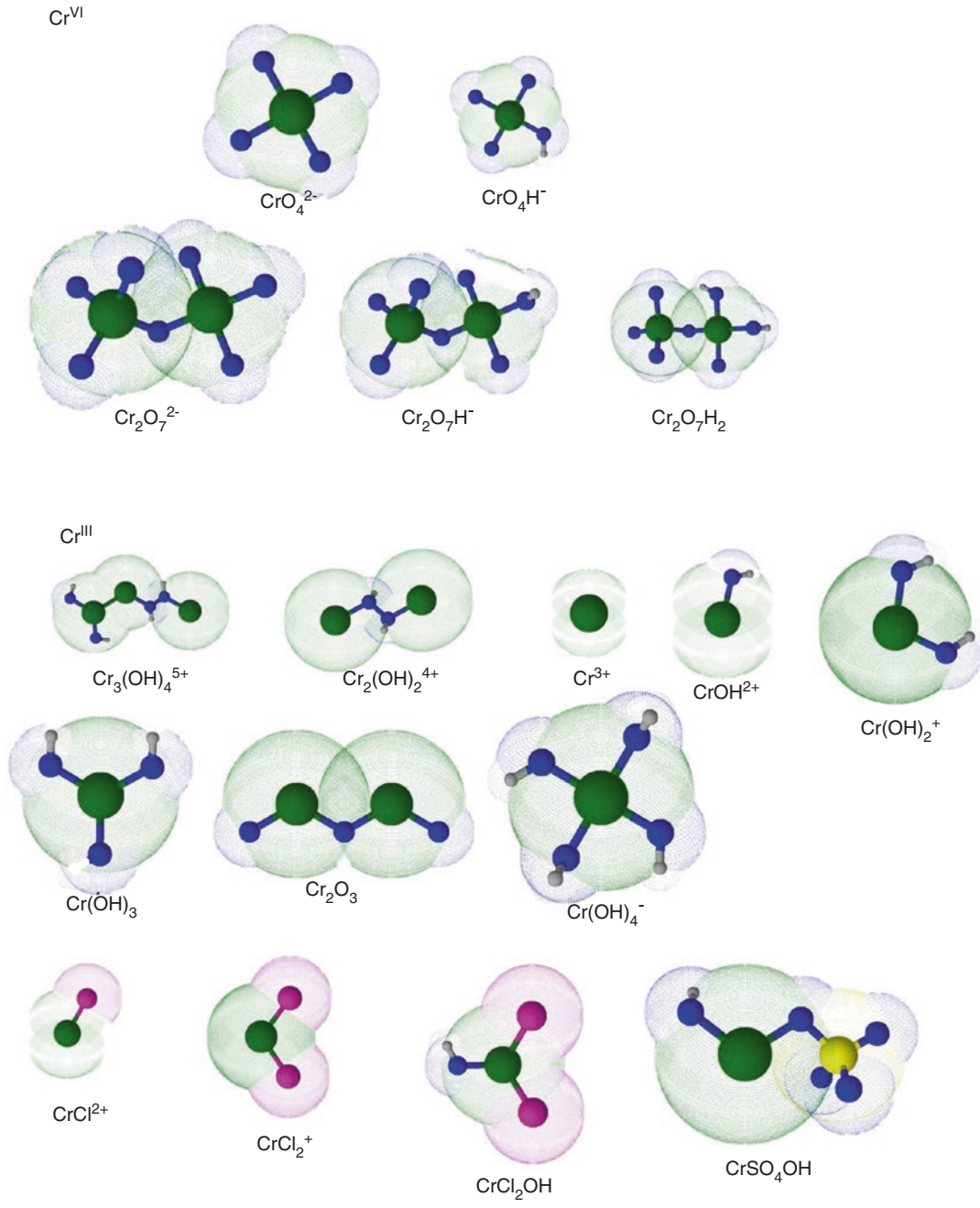

Fig. 27.2 Some examples of relevant cationic, anionic, and neutral hexavalent (*top*) and trivalent (*bottom*) Cr species in aqueous solutions of relevance for patch test solutions and clinical and laboratory studies. Species were analyzed for several patch test solutions (13% $CrCl_3$ and 0.5% potassium dichromate in water) and for the most common leather tanning agent $CrSO_4OH$ in water, using the Medusa software [50], and drawn by the ChemSketch software (ACD/Labs Freeware 2012)

27.3 Skin Deposition

The skin deposition of Cr from different items is not necessarily similar to the amount and chemical form that is released from these items in different simulants, such as artificial sweat. There are two major reasons: (1) most skin contact includes wear processes which are often not considered in laboratory testing, such as in artificial sweat according to the EN 1811 standard [51], and (2) the chemical reactions in skin contact are thin-film reactions and not necessarily comparable to bulk solution conditions [49–52]. It has been shown that the skin deposition on the index finger after touching different metal and alloy surfaces is higher compared with the amount released into artificial sweat [53]. Skin deposition of Cr from different items and in certain occupations has been investigated using acid wipe sampling [54–56] and wipe sampling [57]. The recovery of Cr was between 90% and 102% [58] in acid wipe sampling, however, not tested for Cr^{VI}, which is not possible to distinguish from Cr^{III} using this technique. The skin deposition of Cr has been found to be larger for Cr-tanned leather compared with Cr-containing metal discs [54], which is in accordance with release data (see Use and Sources of Exposure below). It has been highlighted in these studies that even brief skin contact results in significant amounts of deposited metals. This is also true for release processes in bulk solutions, which mostly take place in the first seconds to minutes for passive metals [49, 59] and Cr-tanned leather [60]. With both metals [53] and Cr-tanned leather [61], it was found that surfaces previously stored in air can release more metals compared with previously touched [53] or immersed [61] surfaces. Unpublished results of Cr skin deposition from leather bracelets suggest that Cr is deposited from Cr-tanned leather bracelets (Y. Hedberg, B. Erfani, M. Matura, C. Lidén, unpublished data).

27.4 Skin Penetration

Penetration of Cr through human skin is governed by (1) pH, (2) Cr concentration, and (3) chemical speciation of Cr, as well as biological factors such as the skin barrier (Table 27.1). Since the Cr chemical speciation (Fig. 27.2) is governed by the solution pH, solution composition, and Cr concentration, systematic studies comparing the skin penetration of different Cr compounds are difficult to conduct and interpret. Table 27.1 summarizes several skin penetration studies, with a focus on the comparison of different Cr compounds and solution pH values. Since Cr^{VI} species are generally more soluble at alkaline pH, and Cr^{III} species at acidic pH, they cannot be compared directly without affecting their solubility and ionic charge. It is, however, clear from Table 27.1 and [62] that anionic species of both Cr^{VI} and Cr^{III} penetrate the skin to a larger extent compared with cationic or neutral species. The solution pH affects not only the Cr speciation (which Cr species exist) but also the skin permeability [43] and skin charge [42]. At alkaline pH, both the skin membrane and Cr^{VI} species are negatively charged (Cr^{III} species are not soluble at this pH), which results in electrostatic repulsion and hence no binding. The consequence of the equal skin membrane and Cr^{VI} species charge, as well as the higher skin permeability to water, is that Cr^{VI} species at alkaline pH show the highest Cr skin penetration compared with Cr^{III} species and acidic pH.

27.5 Immunology

In order to be a sensitizer, Cr must bind to a protein (a carrier) to form an antigen [66, 67]. It is now generally accepted that the antigen is a Cr^{III}-protein conjugate and that any Cr^{VI} first needs to be reduced before it binds to a protein [37, 38, 41]. The fact that Cr^{VI} is a stronger sensitizer compared to Cr^{III} (Tables 27.2 and 27.3), even if skin penetration is excluded (e.g., by intra-/subdermal injection or in in vitro assays), may be explained by (1) the strong binding of Cr^{III} to proteins compared with Cr^{VI} and (2) the ability of Cr^{VI} to penetrate the cell membrane and bind to proteins after reduction inside the cell [37, 38, 68]. It has been suggested that Cr (and metal cations in general) changes protein structure upon binding and that this structurally modified

Table 27.1 Relative order of skin penetration rates of different Cr solutions of varying pH values

Order	Skin	Other findings	Reference
$K_2Cr_2O_7$ in water (pH 7–9[a]) > $K_2Cr_2O_7$[b] in artificial sweat (pH 5.5) ≫ $Cr(NO_3)_3 \cdot 9H_2O$ in water (pH 3[c]) ≈ $CrCl_3 \cdot 6H_2O$ in water (pH 3[d])	Porcine and human skin in vitro	Larger amount of Cr^{VI} in skin compared to Cr^{III} (rejection of Cr^{III})	[44]
$K_2Cr_2O_7$ (pH 10, carbonate buffer) > $K_2Cr_2O_7$ (pH 8.8, borate buffer) > $K_2Cr_2O_7$ (pH 6.8, phosphate buffer) ≈ $K_2Cr_2O_7$[e] (pH 5, acetate buffer) $K_2Cr_2O_7$ in water (pH 4.2 or pH 7–9[a]) ≫ $CrCl_3 \cdot 6H_2O$ in water (pH 3) ≈ $Cr(NO_3)_3 \cdot 9H_2O$ in water (pH 2.8) $CrCl_3 \cdot 6H_2O$ in water (pH 3) > $CrCl_3 \cdot 6H_2O$ (pH 8.3, borate buffer) > $CrCl_3 \cdot 6H_2O$ (pH 10.1, carbonate buffer)	Human skin in vitro	Skin penetration of labeled water decreases from pH 10 > pH 8.8 > pH 6.8 ≈ pH 5, but much smaller difference compared with pH dependence of $K_2Cr_2O_7$ penetration	[43]
Percutaneous absorption rate (Na_2CrO_4 in phosphate or NaOH/HCl buffers) higher at pH 6.5–12.8 compared with pH 1.4–5.6[b]	In vivo isotope technique in the guinea pig	Absorption is larger at skin-irritating pH values in buffered solutions (pH 1.5 and 12) compared with non-buffered solutions	[63]
Cr^{VI} aqueous solution (unspecified pH) ≫ $Cr_2(SO_4)_3$ in water (pH 2.6–3.2)	In vitro cadaverous human skin	Skin penetration of Cr^{VI} was similar to that of water; skin penetration of Cr^{III}-sulfate was 10^4 times lower	[64]
$K_2Cr_2O_7$ in water (unspecified pH) > $Cr_2(SO_4)_3$ in water (acidic pH); $K_2Cr_2O_7$ in water (pH 3.9[b]) > $Cr_2(SO_4)_3$ in water (acidic pH)	Isolated dermal human skin; living human skin	Cr^{III} binding to skin membrane, soluble dermis protein, serum albumin, serum globulin, and dry dermis significantly greater compared with Cr^{VI}; Cr^{VI} can be reduced by skin components	[42]
$K_2Cr_2O_7$ in buffered water (pH 7) > $CrCl_3$ in buffered water (pH 7) > $Cr_2(SO_4)_3$ in buffered water (pH 7) ≈ $Cr(NO_3)_3$ in buffered water (pH 7) $CrCl_3$ in buffered water (pH 5) > $Cr_2(SO_4)_3$ in buffered water (pH 5) > $Cr(NO_3)_3$ in buffered water (pH 5) $CrCl_3$ in buffered water: pH 9 > pH 5 > pH 7 $Cr_2(SO_4)_3$ in buffered water: pH 5 > pH 9 > pH 7 $Cr(NO_3)_3$ in buffered water: pH 7 ≈ pH 5 > pH 9	Isolated human epidermis	Among the Cr^{III} salts, $CrCl_3$ in phosphate-buffered water had the largest fraction of anionic species compared with $Cr_2(SO_4)_3$ and $Cr(NO_3)_3$	[62]
$K_2Cr_2O_7$ in petrolatum > $K_2Cr_2O_7$ in water > Cr^{III}-glycine in water	Living human skin	–	[65]

[a]Estimated from Medusa calculations [50] and own measurements. Not in agreement with pH reported in [43] (pH 4.2)
[b]A (significant) part of Cr^{VI} is expected to be reduced to Cr^{III} in this solution(s), a time-dependent process
[c]Estimated from pH reported in [43]
[d]Estimated from pH reported in [43] and Medusa calculations
[e]A significant part of Cr^{VI} is expected to be reduced to Cr^{III} and complexed to acetate in this solution

Table 27.2 Relative order of magnitude of positive skin reactions in Cr-sensitized persons to Cr solutions of varying pH

Order	Number of tested persons	Results (allergic reactions)	Reference
$K_2Cr_2O_7$ in water (unspecified pH) > $Cr_2(SO_4)_3$ in water (acidic pH)	40 Cr-sensitized persons	40/40 positive to 20 μL of 0.01% $K_2Cr_2O_7$ and 20/40 positive to 0.001% $K_2Cr_2O_7$ (intracutaneous injection). No positive reactions up to 1% $Cr_2(SO_4)_3$ (intracutaneous injection)	[42]
$K_2Cr_2O_7$ in water > $Cr_2(SO_4)_3$ in water ≈ $CrCl_3$ in water > $Cr(NO_3)_3$ in water (intact skin); $K_2Cr_2O_7$ in water > $Cr(NO_3)_3$ in water ≈ $CrCl_3$ in water > $Cr_2(SO_4)_3$ in water (stripped skin)	4–5 Cr-sensitized persons—patch testing	Stronger reactions to Cr^{III} compounds for stripped skin compared with intact skin; no difference for Cr^{VI}	[82]
$K_2Cr_2O_7$ in water > $CrCl_3{\cdot}6H_2O$ in water (patch testing) $K_2Cr_2O_7$ in water ≈ $CrCl_3{\cdot}6H_2O$ in water (intracutaneously)	17–22 Cr-sensitized persons	Intracutaneous test results of Cr^{III} are comparable with Cr^{VI}; skin penetration important for epicutaneous tests	[83]
$K_2Cr_2O_7$ in water > K_3-Cr^{III}-oxalate in water > Cr^{III}-acetate in water (patch testing); $K_2Cr_2O_7$ in water > K_3-Cr^{III}-oxalate in water > $CrCl_3$ in water > Cr^{III}-acetate in water (intracutaneously)	14–35 Cr-sensitized persons	Patch test results: 35/35 reacted positively to 0.01 M $K_2Cr_2O_7$, 29/35 to 0.05 M K_3-Cr^{III}-oxalate, and 7/35 to 0.5 M Cr^{III}-acetate	[84]
$K_2Cr_2O_7$ in water (pH 7–9[a]) > $CrCl_3{\cdot}6H_2O$ in water (pH 2.2)	18 Cr-sensitized persons—patch testing	Reported in Table 27.3	[85]
$K_2Cr_2O_7$ in water (pH 7–9[a]) > $CrCl_3$ in water (pH 2.2)	2211 persons (unknown Cr sensitization)—patch testing	3.2% reacted to Cr^{VI} and 1.4% to Cr^{III}. None reacted to Cr^{III} without reacting to Cr^{VI}	[86]
$K_2Cr_2O_7$ in water (pH 7–9[a]) > $CrCl_3$ in water (pH < 3–4[a])	14 Cr-sensitized persons—patch testing	Reported in Table 27.3	[87]
$K_2Cr_2O_7$ in water > $Cr(SO_4)OH$ in water (pH 3)	94 Cr-sensitized persons—patch testing	70/94 reacted positively to 0.1 M $Cr(SO_4)OH$	[88]
$K_2Cr_2O_7$ in water (irritated skin by sodium lauryl sulfate, patch testing) > $K_2Cr_2O_7$ in water (intact skin, patch testing) > $K_2Cr_2O_7$ in water (intact skin, repeated open application test (ROAT))	17 Cr-sensitized persons	Patch test threshold for intact skin, 10 ppm Cr^{VI}; for irritated skin, 1 ppm Cr^{VI}; in ROAT, 3/15 reacted positively to the lowest concentration of 5 ppm Cr^{VI}	[78]

[a]Estimated from Medusa calculations [50] and own measurements

protein is processed and presented to T cells by cutaneous dendritic cells (Langerhans cells) [67] (sensitization step) or recognized by circulating hapten-specific T cells (elicitation step) [66, 67, 69, 70]. Activation of human monocyte-derived dendritic cells through direct ligation with human Toll-like receptor (TLR)-4, shown to be important for nickel, palladium, and cobalt, has not been found to be important for Cr [71]. It is well known that Cr^{III} can modify protein structure, or even strongly aggregate proteins, such as normally pure serum albumin [45–47, 72]. Whether this structural modification or any other reaction is responsible for the antigenic properties is unclear. Several Cr^{III}-protein conjugates have been identified that are able to be recognized as antigen by Cr-sensitized persons (investigated by different methods), in decreasing order: human serum albumin [73–76], heparin [75, 76], hyaluronic acid from human umbilical cord [76], undefined skin proteins [73], and γ-globulin [74, 75].

Generally, due to the strong effect of skin penetration (for all Cr species) and protein binding

Table 27.3 Minimum elicitation threshold (MET) values of Cr^{III} or Cr^{VI} solutions of different studies, all through occluded patch testing on intact skin for 48 h, on Cr-sensitized persons

Solution	MET[a] in µg/cm² (ppm)	$MET_{10\%}$[b] and $MET_{50\%}$ in µg/cm² (ppm)	Reference
Cr^{III}			
$CrCl_3 \cdot 6H_2O$ in water (pH ≥ 2.2)	1.5 (50)	0.18 (6), 2.7 (89)	[85]
$CrCl_3$ in water (pH < 3–4[c])	4.4 (88.5)	n.r.	[87]
$CrCl_3$ in gel (pH n.r.)	33 (n.r.)	n.r.	[89]
Cr^{VI}			
$K_2Cr_2O_7$ in water (pH 7–9[c])	0.06 (2)	0.03 (1), 0.15 (5)	[85]
$K_2Cr_2O_7$ in water (pH 7–9[c])	0.45 (8.9)	n.r.	[87]
$K_2Cr_2O_7$ in water (pH 7–9[c])	0.56 (28)	n.r.	[90]
$K_2Cr_2O_7$ in gel (pH n.r.)	0.018 (n.r.)	0.089 (n.r.), n.r.	[89]

Values are reported as µg Cr per cm² (skin dose), which for some references had to be calculated based on available area and volume information, and as concentration (ppm Cr)

n.r. not reported

[a]The MET value is here defined as the lowest Cr concentration that resulted in a positive reaction in this study

[b]The 10% and 50% MET values are calculated mathematically using dose-response curves

[c]Estimated from Medusa calculations [50] and own measurements

(in the case of Cr^{III} only), allergic responses are greater for sub- or intracutaneous testing relative to epicutaneous testing, as well as irritated or stripped skin relative to intact skin (Table 27.2). Furthermore, skin penetration largely determines the wide variation among the different Cr solutions summarized in Table 27.2. However, for anionic Cr^{III} solutions, such as Cr^{III}-oxalate, the difference from Cr^{VI} solutions is smaller (Table 27.2). Several minimum elicitation threshold values for Cr^{III} and Cr^{VI} are summarized in Table 27.3, and other studies are summarized in [77]. These were obtained via occluded patch testing, and it has been argued that more realistic methods such as repeated open application tests (ROAT), where the test solution is applied for brief discontinuous periods on non-occluded skin, are needed. ROAT tests have been conducted for aqueous potassium dichromate solutions, where comparable threshold values were obtained as in occluded patch tests [78, 79].

Concomitant reactivity to other haptens may occur, possibly due to cross-reactivity or co-sensitization. For example, concomitant reactivity to Cr and Co has been observed [80]. A recent study on 656 consecutive dermatitis patients, of which 200 patients reacted positively to either Co, Cr, or Ni, demonstrated that reactivity to each of these metals can either exist independently or for one or several more metals, suggesting co-sensitization rather than cross-reactivity to be the reason behind concomitant reactivity [81].

27.6 Use and Sources of Exposure

Cr is used or present in a large variety of articles, products, and alloys. In contrast to other metal allergens, the most important sources of skin exposure, both occupationally and environmentally, are nonmetals: Cr-containing cement, Cr-tanned leather [86, 91], and different fluids and chemicals, such as detergents and bleaching chemicals [92]. Table 27.4 summarizes amounts of released Cr^{III} and Cr^{VI} from different sources into select environments. Generally, the release of Cr from noncorroding metals and alloys is significantly lower compared with Cr-tanned leather (Table 27.4). The release of Cr from noncorroding metals is not proportional to their Cr content, which is also illustrated in Table 27.4. Corroding metals and alloys can, however, release a significant amount of Cr^{III}. Corroding metals and alloys without any chromate-containing coatings can only release significant amounts of Cr^{VI} if a high voltage is applied (Table 27.4), which does not occur in ambient environments, skin contact, or the human body, but might be important in certain manufacturing processes, electrical applications, or implants that make use of high pulsed voltage. Chromate coatings have been used as anti-fingerprint coating on metal surfaces during transport and storage, such as roof sheets, screws, and other metal products [93]. These coating

Table 27.4 Reported release of Cr^{III} and Cr^{VI} (μg) per surface area of different sources (cm^2)

Category of source material	Source	Environment/solution	Release of Cr^{III} (μg/cm^2)	Release of Cr(VI) (μg/cm^2)	Reference
Coatings on metals	Chromate coating on galvanized steel	Artificial sweat	Not tested	<0.005 (LOD)–**0.60**	[99]
	Chromate containing anti-fingerprint coating on galvanized steel	Rain water	<0.007	<0.004	[93]
	Cr_2O_3 containing anti-fingerprint coating on galvanized steel	Rain water	<0.0003	<0.00002 (LOD)	[93]
Metals	Chromium and Cr_2O_3 (powder and sheet)	Synthetic body fluids, pH 1.5–8.0	<0.02	<0.0003 (LOD)	[48, 100–102]
	Iron powder	Synthetic body fluids, pH 1.5–4.5	0.04 (pH 4.5) **0.2** (pH 1.5)	<0.0002 (LOD)	[100, 103]
Biomedical and engineered alloys	Stainless steel, ferrochromium, and ferrosilicon chromium alloy (powder and sheet)	Synthetic body fluids, pH 1.5–8.0	<0.08	<0.0002 (LOD)	[48, 96, 100–102, 104, 105]
	Low chromium and 13Cr/12Ni—stainless steel (possibly corroding)[a]	Artificial sweat and 0.9% saline	**0.9–5.6**	<0.01 (LOD)	[106]
	Nickel-chromium alloy (possibly corroding)[a]	Artificial sweat and 0.9% saline	**0.6–4.2**	<0.01 (LOD)	[106]
	Cobalt-chromium-molybdenum alloy for joint prostheses	Synthetic body fluids	<0.01	<0.00005 (LOD)	[96]
	Cobalt-chromium-molybdenum alloy, strongly oxidized	Phosphate-buffered saline	About **0.3–5**	About **1–6**	[96]
Welding fume	Stainless steel welding fume particles	Alkaline extraction solution	Not tested	320–3000 μg/g (0.01–**0.15**[b] μg/cm^2)	[107]
Leather	Chromium-tanned leather containing antioxidants	Artificial sweat, phosphate buffer	**0.3–72**	<0.1 (LOD)	[60, 108]
	Chromium-tanned leather with low amounts of antioxidants	Artificial sweat, rain, phosphate buffer, alkaline solution	**2–60; 2–7; 0.4–9; 8–12**	<0.06 (LOD); <0.06 (LOD); <0.06 (LOD)—**0.6**; **0.3–0.5**	[60, 108, 109]
	Chromium-tanned leather with low amounts of antioxidants, after 7.5 months of simulated use	Phosphate buffer	**0.5**	**0.6**	[61]
	Chromium-tanned leather mobile phone case	Phosphate buffer	**2.2**	**0.2**	[c]
	Chromium-tanned leather work gloves	Phosphate buffer	**0.8–1.7**	**0.1–0.3**	[109, 110]
	Purely vegetable-tanned leather	Artificial sweat, phosphate buffer	<0.1 (LOD)	<0.1 (LOD)	[60, 108]

Table 27.4 (continued)

Category of source material	Source	Environment/solution	Release of Cr^{III} (μg/cm²)	Release of Cr(VI) (μg/cm²)	Reference
Cement	Wet cement and wastewater after cement contact	Artificial sweat, water	<0.0001 (LOD)	Approx. 2 mg Cr(VI)/kg; 0.0003[d] μg/cm²	[111]

Only studies that distinguished between Cr^{III} and Cr^{VI} and reported the amount per surface area are summarized in the table. For clarity, values exceeding 0.18 μg Cr^{III}/cm² and 0.03 μg Cr^{VI}/cm² (observed 10% minimum elicitation threshold values for 2-day patch testing in [85]) are marked in bold. Note that important experimental conditions, such as extraction duration, are not reported in this table but in the referred publications

LOD limit of detection

[a]It is not explicitly mentioned in this reference [106] whether the samples were corroding, but the relatively high amounts of chromium and nickel release reported, as well as the strongly accelerating release with time, suggest this

[b]Assuming a specific surface area of 2 m²/g

[c]Unpublished results (Y. Hedberg); analysis as in [110]

[d]The release in μg/cm² is recalculated from the data by assuming a specific surface area of the cement of 1 m²/g [112]

types can result in Cr^{VI} release upon skin contact when a product is new or has been stored at dry conditions, and they are increasingly replaced by manufacturers with alternative coatings [93]. Cr-releasing particles include welding fume from Cr-containing alloys and cement particles (Table 27.4). Since ultrafine particles can be inhaled and reach the alveolar region in the lung [94], special protection is required. Certain combinations of exposure factors and source chemistry should also be avoided. These include for Cr-tanned leather (Table 27.4): (1) alkaline fluids such as wet cement contact or detergents, (2) dry storage in low humidity followed by wet skin exposure, and (3) frequent skin contact with Cr-tanned leather that was not treated with antioxidants.

Cr can also be released from Cr-containing alloys (nearly all implant materials that require wear and corrosion resistance) inside the human body, such as from different stainless steel and cobalt-chromium-alloy dental or artificial joint prostheses. The released form is ionic Cr^{III} or wear particles including Cr^0 or Cr^{III} in the form of Cr_2O_3 [95, 96].

Other sources vary largely among countries and occupations and depend on prevailing safety procedures, technologies, and regulations. Industrial/professional use includes chromate containing anticorrosion inhibitors or coatings, catalysts (Cr^{III} based and converted to other oxidation states during the process), electroplating (CrO_3) and anodization agents, pigments (green Cr_2O_3, decreasingly yellow/orange chromates) for the production of glass or ceramics, chromates in paints, mordant dyes of textiles, Cr^{VI}-containing wood preservatives that are converted to Cr^{III} during the process, Cr^{VI}-containing oxidative bleaching chemicals, and wet cement [4, 97, 98].

Green pigments in cosmetics and tattoo ink (Cr_2O_3); Cr-containing ash, e.g., due to combustion of Cr-tanned leather and preserved wood; and dry/wet cement are examples of other sources that are not necessarily an occupational exposure [4, 70, 92, 97, 98]. A more detailed summary of different sources, including older technology and processes, can be found in [4].

27.7 Clinical Manifestations

27.7.1 Contact Dermatitis

Contact dermatitis to Cr is often located on the hands and feet [86, 113]. Cr dermatitis is associated with greater severity of hand eczema [114], a lower quality of life [115], and higher prevalence of sick leave [115], compared to other dermatitis patients. Cr contact dermatitis is very persistent [116, 117] and has a poor prognosis [113–115, 118–120]. It has been suggested that

this might be due to the multitude of different Cr sources and/or an ability of Cr to remain absorbed in the skin [116, 117]. However, it has been shown that strict allergen avoidance, mainly by a change of workplace or early retirement, resulted in the improvement of 72% of Cr contact dermatitis patients' symptoms within a few years [121]. Systemic contact dermatitis is not very common and of minor importance, except in the setting of a high oral intake of Cr^{VI} [97] and Cr^{III} food supplements [122].

27.7.2 Hypersensitivity to Implant Materials and Their Wear Debris

In regard to the general prevalence of metal contact dermatitis, nickel and cobalt are more commonly reported to cause hypersensitivity reactions compared with Cr [123]. However, Cr is an alloying element in many biomedical metallic implant materials and might be released in nano-sized wear particles [95] or as ionic species (Cr^{III}) [96]. Cr ions or Cr-containing wear debris released from implant materials can cause cutaneous allergic reactions [123–125], peri-implant inflammation [123, 126], and other reactions [127]. Large aggregates of Langerhans cells have been found in the lymph nodes of a patient with high cobalt and Cr serum ion levels [124], suggesting a type IV (cell-mediated) reaction. Complications for patients with articulating implants, especially knee arthroplasty, are associated with a higher rate of metal sensitization [123]. It is, however, unclear whether the metal sensitization caused complications or vice versa [123]. Symptomatic relief and/or disappearance of associated eczema has been reported after replacement of the implant, but the role of metal allergy is still not clear for several other complicating conditions (e.g., persistent pain, aseptic loosening, pseudotumors) [123]. Two studies concluded that the overall risk of knee arthroplasty failure is not increased due to metal hypersensitivity [128, 129]. It was also shown (in 52 patients) that, despite higher serum ion levels as compared to metal-on-polymer implants, having cobalt- and Cr-releasing metal-on-metal hip implants did not increase the prevalence of Cr or cobalt contact dermatitis after a 5-year follow-up [130]. This was confirmed in a Danish registry-based study, where it was, however, found that the prevalence of cobalt and Cr contact dermatitis was increased for patients having two or more episodes of revision surgery [131].

27.7.3 Allergic Asthma

Asthma is a common disease worldwide, with a physician-diagnosed prevalence rate of 4.3%, ranging from 0.19% (China) to 21% (Australia) [132]. Its prevalence is not declining [133]. The incidence of allergic asthma is approximately equal to that of non-allergic asthma, but dependent upon age [134]. Cr-induced allergic asthma has been reported relatively scarcely [135] for some occupations, such as welding, electroplating/metal plating, and cement work [136–139]. It has been suggested that the metal sensitivity involved in allergic asthma may be IgE mediated without a clear association with allergic contact dermatitis to the same metal [135, 138, 140] or may be IgE mediated in some cases, but not in others [136, 139]. Thus, there is some evidence for both delayed and immediate types of allergic asthma to Cr.

27.8 Patch Testing, Spot Testing, and Other Testings

For patch testing, potassium dichromate 0.5% in petrolatum (e.g., baseline series for Europe) or 0.25% in petrolatum (e.g., North America) is most often used [97]. These Cr^{VI} patch test allergens can cause irritant reactions that are sometimes difficult to distinguish from allergic reactions without retesting. However, lower concentrations of Cr^{VI}, shorter patch test durations than 48 h, or the use of Cr^{III} salts may instead result in a large percentage of false negatives (Tables 27.2 and 27.3) [90]. A recent study found that Cr was associated with a significantly higher percentage of potentially irritant reactions for at

least one patch test reading (day 3 or days 6–7 after the start of patch test placement for 48 h), in comparison to cobalt and nickel [81]. It seems, therefore, particularly important that two readings be conducted when patch testing to Cr [81]. Of note, the number of irritant reactions for Cr patch testing increased with lower temperature and lower humidity [141], probably related to an impaired skin barrier under these conditions. For children, the same patch test concentration as for adults (0.5% potassium dichromate in petrolatum) was recommended, if there was a history of reactions to shoe allergens [142]. In addition to patch testing, less commonly used tests are immersion tests [143] and repeated open application or prolonged tests [79, 91].

In order to identify potential sources of Cr in a simple and inexpensive way, Cr^{VI} spot testing using diphenylcarbazide (DPC) has been suggested and conducted [4, 144, 145]. The test is, however, more challenging to interpret and conduct correctly, as compared to other spot tests such as for nickel and cobalt. This is due to its specificity to Cr^{VI}, relatively high detection limit of 0.5 mg/L Cr^{VI} [145], and the potential loss of specificity to Cr^{VI} upon oxidation in air, facilitated by illumination [146]. Cr^{VI} is easily reduced to Cr^{III} on many surfaces, including leather and metal surfaces, at a sufficiently high relative humidity in air [61, 93, 109]. The DPC spot test can hence miss Cr^{VI} that has been reduced to Cr^{III}, but may be oxidized again on leather surfaces when the relative humidity is low [61, 109]. The DPC spot test may furthermore miss lower Cr^{VI} concentrations and all Cr^{III}, which are also able to cause positive reactions (Tables 27.2 and 27.3). Despite these limitations, the DPC spot test might be a reasonable initial rapid screening tool, and contact with items that test positive should be avoided for a Cr-sensitive person.

Currently, other tests cannot be performed as easily and inexpensively. X-ray fluorescence can detect the total Cr content of a product, but does not give information on its potential Cr release, which often differs (Table 27.4). Release tests can be very relevant and should ideally be able to distinguish between Cr^{III} and Cr^{VI} (speciation testing). Candidates for speciation testing are the DPC test by means of spectrophotometry (UV-vis), testing by means of stripping voltammetry (polarography), and distinction by chromatography techniques, before/in conjunction with analytical techniques for total Cr such as atomic absorption spectroscopy and inductively coupled plasma spectroscopy [147]. The DPC spectrophotometry test is used both in standard Cr^{VI} testing in cement [148] and in leather [149]. More details on the testing of Cr^{VI} in leather can be found in Chap. 4.

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Metal Allergy: Cobalt

28

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28.1 Introduction

Cobalt is a metal with a silvery appearance, mainly mined in Africa where it is found in ores rich in nickel and copper. Due to its special properties such as ferromagnetism and high resistance to heat and wear, cobalt is widely used in many different applications. Cobalt has a well-known toxicity to humans. It is a potent skin sensitizer and one of the most common causes of contact allergy in humans [1]. Inhalational exposure to cobalt can lead to respiratory diseases such as asthma and, in highly exposed individuals, also interstitial lung fibrosis [2]. Soluble cobalt (II) salts and cobalt metal are classified as possibly carcinogenic to humans (group 2B), whereas cobalt metal in combination with tungsten carbide is classified as probably carcinogenic to humans (group 2A) by the International Agency for Research on Cancer (IARC) [3]. Consequently, occupational respiratory exposure to cobalt is regulated in several countries by occupational exposure limit (OEL) values that are established to prevent lung cancer. However, no OELs exist for skin exposure to cobalt.

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28.2 Immunology, Sensitization and Diagnostic Tools

A prerequisite for the development and manifestation of contact allergy, a delayed-type IV hypersensitivity reaction, is direct contact of the skin with an allergen. For cobalt to become an allergen, cobalt ions must penetrate the skin and bind to a carrier protein. This ion-protein complex can then interact with toll-like receptor 4 (TLR-4) on dendritic Langerhans cells (LC). The LC will migrate to the lymph nodes, where allergen-specific T-cells are activated, proliferate and mature. This process is described as the *induction* of contact allergy, which is the phase where the immune system adapts to recognize the allergen. Once activated, allergen-specific memory T-cells will reside in the skin, causing an inflammatory response upon re-exposure to the allergen, i.e. the *elicitation* phase of the contact allergy, giving the clinical disease of allergic contact dermatitis [4]. To study elicitation, testing in already sensitized individuals is an option, which may be used after ethical vetting. It has been shown that the amount (μg) of allergen and the skin surface area exposed (cm^2) to the allergen are of great importance for the development of contact allergy [5].

The sensitizing potential of a substance is evaluated using animal models. One such model is the murine local lymph node assay (LLNA). Using the LLNA, it was shown that cobalt chloride ($CoCl_2$) is a potent sensitizer [6]. Another

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assay that has been used is the guinea pig maximisation test (GPMT), which has also shown that $CoCl_2$ is a strong sensitizer (grade V) [7, 8]. Using the GPMT has further shown that animals induced by $CoCl_2$ did not react when challenged with nickel sulphate or potassium dichromate, supporting the hypothesis that multiple sensitization occurs rather than cross-reactivity, which is important for the interpretation of human patch test data.

For animal ethical reasons, much research is currently focused on developing in vitro models for testing the sensitizing potential of chemicals. So far, three methods have been approved by the European Union Reference Laboratory for Alternatives to Animal testing (EURO ECVAM): the Direct Peptide Reactivity Assay (DPRA), the KeratinoSens™ and the Human Cell Line Activation Test (https://eurl-ecvam.jrc.ec.europa.eu/validation-regulatory-acceptance/topical-toxicity/skin-sensitisation#1-ecvam-validated-test). These in vitro methods address single key events in the adverse outcome pathway (AOP) of skin sensitization. Therefore, none of the current in vitro assays can by themselves substitute for the animal test due to the complexity of the skin sensitization endpoint. Future assessment of skin sensitization using nonanimal methods will need an integrated test strategy, based on the combinations of several in vitro tests for different key events and read-across.

28.3 Patch Testing

Cobalt allergy in humans can be verified by the patch test, the diagnostic tool for contact allergy. The test substance is applied onto the upper back of the patient using a closed chamber to contain it. If the person is sensitized, this will elicit allergic contact dermatitis at the test site [9]. The European patch test baseline series contain 1% cobalt chloride ($CoCl_2$) in petrolatum, but aqueous solutions can also be used. Other test systems and several different national series exist: one example is the T.R.U.E. test with a predefined skin dose of 20 μg/cm^2 of the test substance (cobalt dichloride hexahydrate $CoCl_2 \cdot 6H_20$, corresponding to 4.9 μg Co/cm^2).

When it is of interest to evaluate the sensitivity of a patient, serial dilutions may be used, although this is not recommended for routine use. The method of serial dilution patch testing is usually performed for research purposes to establish elicitation thresholds of an allergen [10] or to establish how an allergic response varies over time [11]. In a recently published study, the elicitation dose for cobalt was calculated by applying a logistic dose-response model to six serial dilution patch test studies [10]. The results showed that the elicitation dose of cobalt was within the range of 0.0663–1.95 μg/cm^2 for 10% of the patients and from 1.45 to 17 μg/cm^2 for 50% of the patients [10]. Other ways of testing include using, for example, metal discs of different alloys to evaluate whether they might cause dermatitis. For cobalt, this has been done using different hard metal alloys, to establish if they could elicit dermatitis in cobalt allergic patients [12]. Data like these are important for risk assessment and for the comparison of skin doses of cobalt in healthy individuals or in exposed workers.

It has been stated that patch testing with 1% $CoCl_2$ will give rise to false-positive reactions such as follicular, petechial and 'poral' patch test results that are sometimes described as difficult to interpret [13, 14]. However, patch testing with lower concentrations than 1% of $CoCl_2$ in aqueous solution was shown to reduce the number of positive reactions in six patients [15]. In Sweden, patch testing using the national base line series with $CoCl_2$ at 0.5% in aq. has been used since around 1985, due to reports of the risk of false-positive reactions. In a recent study from Sweden, 656 consecutive dermatitis patients were concomitantly patch tested with both 1% and 0.5% $CoCl_2$ in aq. [16]. The study showed not only that solitary cobalt allergy was prevalent, with 50% of the cobalt allergic patients having a solitary reaction, but also that the proportion of false-positive reactions was of the same magnitude for both concentrations tested. Solitary cobalt allergy has also been shown in studies from Germany, where the prevalence was

41% and 42% [17, 18]. In a study of 16-year-old adolescents in the general population ($n = 2285$), it was more common to find solitary cobalt allergy (62%) than concomitant allergy with nickel or chromium [19]. Current data show that cobalt allergy can be solitary and not only found concomitantly with nickel or chromium. To evaluate the relevance of solitary cobalt patch test results, improved knowledge of cobalt exposures is a prerequisite.

28.4 Prevalence of Cobalt Allergy

Contact allergy to cobalt is common in dermatitis patients in general but more pronounced among specific occupational groups. Among dermatitis patients, numbers range from 4.5% to around 11% for studies from Europe and North America [20–25]. Cobalt is also a frequent sensitizer among adolescents of the general population in Sweden and Denmark [19, 26]. The prevalence of cobalt allergy in the general population of adults and adolescents ranges from 0.2% to around 1.2% (Table 28.1) [19, 26, 27]. Women generally have higher prevalence numbers than men, but the gender difference is not of the same magnitude as for nickel allergy.

There are many reports of cobalt allergy among occupational groups. Some of the most well-known include hard metal workers [32], pottery and porcelain workers [33–35] and construction workers [36–38]. Reports are also available of cases from animal feed handling, offset printing, metal working fluids and polyester resins [39–43]. Cobalt allergy among these occupations typically ranges from 4% to 20%. Among cement workers in Taiwan, cobalt allergy was reported at 4.2% and from Swedish hard metal production workers at 4.6% [44, 32]. In construction workers from Germany and Austria 8.6% were reported to have cobalt allergy [36], while even higher numbers were reported among electronics workers in Taiwan (9.8%) and dental technicians in Korea (12%) [45, 46]. Cobalt allergy was present at 4% among all reported cases of occupational contact dermatitis in the UK [47], whereas in

Table 28.1 Examples of prevalence (%) of cobalt allergy among dermatitis patients and the general population from different countries in Europe and from North America

Country/region	Period	*n*	Prevalence of cobalt allergy (%)			Reference
			Total	Women	Men	
Dermatitis patients						
Sweden	1992–2000	3790		7	9	[28]
Spain	2000–2005	1092	10.8	8.3	2.4	[20]
Denmark	2004–2009	9138		5.2	2.2	[29]
Sweden	2009	3112	4.5	<40 year: 6.4 >40 year: 5.2	<40 year: 2.6 >40 year: 2	[21]
Europe	2005–2006	19,793	6.2–8.8			[23]
Europe	2009–2012	56,826	6.5			[22]
North America	2009–2012	4303	6.2			[24]
North America	2011–2012	4231	7.3			[25]
General population						
Denmark	1990–2006	3460	0.2	0.4	0.1	[27]
Denmark[a]	1995–1996	1146	1.0	1.5	0.6	[26]
Europe	2008–2011	3119	2.2	3.0	1.1	[30]
Denmark	2010	442	2.3	3.3	0.6	[31]
Sweden[b]	2011–2013	2285	1.2	1.2	1.13	[19]

[a]Adolescents 12–16 years
[b]Adolescents 16 years

Germany, 20% were reported to have contact allergy to cobalt from the registered cases of occupational skin disease among construction workers [48].

28.5 Sources of Cobalt Exposure

Cobalt has been used as a pigment for colouring glass and pottery for more than 4000 years. Cobalt and cobalt compounds are frequently used in different industries where skin exposure occurs. The main application groups are metallurgy (superalloys, wear-resistant coatings, prosthetic alloys, etc.), magnetic alloys (hard and soft magnets), chemicals (batteries, catalyst driers and pigments, colours, agriculture and medicine, etc.), cemented carbides (hard metal tools for cutting and grinding, metal forming, mining: rock drills, etc.), cobalt-bonded diamonds (for cutting stone and grinding diamonds), electronics (recording material, expansion—alloys, batteries) and ceramics and enamels (mainly as colours in glass, enamels, pottery and china) [49].

A special application for cobalt is in metal implants for hip replacements, knee arthroplasty or different dental implants and oral restoration structures made from different cobalt-chromium alloys (see Chap. 27). The failure of such implants due to misfit, stress or fatigue and consequently the release of cobalt or chromium inside the body has been suggested to cause allergy to metal implants. However, the mechanism behind possible immunological effects induced by cobalt alloy debris particles is not clearly understood [50]. In a recent study, however, it was suggested that the implant-related immune effects of cobalt alloy particles were not due to stimulation of TLR-4 but rather due to stimulation of the innate immune response through NLRP3 inflammasome danger signalling [51]. Hence, it seems that a different response is more active compared to the type IV hypersensitivity mediating contact allergy of the skin.

Dental prosthesis alloys made from cobalt-chromium or different nickel compositions have been reported to cause hypersensitivity [52]. Often the patients' symptoms disappear after the prosthesis has been removed, but it is not always possible to prove that the prosthesis released any of the metals [53]. It has been shown, though, that the materials and prostheses do release cobalt during manufacturing and from the alloys used to make them [52–54]. Also, the release of cobalt from a dental implant was verified by the cobalt spot test in a case from Denmark, where the patient's problems disappeared after changing the material in the implant [55].

Except for certain occupational exposures to cobalt, little is known about cobalt exposure, particularly in the general population and in younger age groups. Below, a description of the most well-known exposures thus far to workers and consumers is presented. Given that there is still very limited information available on cobalt exposure, it is important that all professionals that meet cobalt allergic patients, including dermatologists, occupational physicians, chemists and occupational hygienists, thoroughly investigate the sources of cobalt exposure. Several tools exist, such as the cobalt spot test (using 30–50 μL/tops to perform the test), ingredient labelling, safety data sheets and release tests followed by chemical analysis.

28.5.1 Occupational Exposure

Workers within the metal manufacturing and machining industries as well as construction workers can be exposed to cobalt on the skin when processing or handling materials or tools during production. One example of exposure to cobalt is from the production of superalloy components used for jet engines, gas turbines and space propulsion, where the alloy must withstand very high temperatures. Skin exposure to cobalt occurs during the different production steps of these structures, either due to direct contact with the material or from particles deposited on the skin that are generated during the machining or grinding processes. In a study from 2010, it was shown that cobalt skin doses in the range of 0.001–4.5 μg Co/cm^2/h were present on the hands

of workers in a facility producing such superalloy structures [56]. These levels are in the ranges known to be able to elicit cobalt dermatitis.

Several studies have shown that cobalt allergy among construction workers is common, although clear sources of exposure have not always been pinpointed or the skin dose measured. It is, however, clear that cement work, brick laying work, paint work and polyester resin work may give rise to a cobalt allergy [37–39]. In a study from Northern Bavaria, Germany, it was found that cobalt allergy was the third most prevalent allergy after chromium and epoxy resins among construction workers. In total, 20% of patch tests were found to be positive to cobalt chloride ($CoCl_2$), and out of these positive reactions, 48% were occupationally relevant reactions [37]. It has also been shown that cobalt allergy is frequent (9%) and often associated with chromium allergy (20%) in construction workers [36].

Another example of occupational exposure to cobalt is found in dental technicians who are subjected to cobalt when producing different types of prostheses and metal constructions for dental crowns and other oral restoration structures. Often, the dental alloys consist of cobalt-chromium combined with other metals added as minor alloying elements. These alloys release cobalt and chromium upon handling and shaping [54]. In a recently published paper, it was shown that dental technicians are exposed to cobalt on the skin in concentrations that would be able to elicit contact dermatitis in already sensitized individuals [57].

Workers in hard metal facilities are also known to be exposed to cobalt, sometimes in very high concentrations, both through airborne and skin contact from touching raw materials (powders) and from handling produced items [58] (Jolinde Kettelarij, personal communication).

28.5.2 Consumer Exposure

Cobalt is present in several different items that are mainly used by consumers, such as jewellery, leather, cosmetics and electronics [1]. Regarding jewellery, it has been proposed that cobalt would be mostly found in cheap items with a dark appearance [59, 60]. A study from Korea, investigating nickel and cobalt release from jewellery, showed that the majority of cobalt spot test-positive items were found among light-appearing brand items, i.e. not dark and cheap jewellery [61]. It seems more likely that cobalt, which is an expensive metal with a white silvery appearance, would be used more in light-coloured items that are not primarily sold in street markets. In the Korean study, cobalt was also present in clothing details, which, at present, has not been studied thoroughly.

Cobalt pigments may also be used as ingredients in cosmetics such as powders, eyeliners and nail sculpting polishes [62]. In recent case reports, dermatitis has been shown to be caused by artificial nail sculpturing, which was first considered to be caused by acrylates [63, 64]. After further investigation, however, the dermatitis was shown to be due to cobalt used for a glittering polish in one case and for a magnetic polish in another case.

Metal exposure from contact with leather has mostly been studied from the chromium point of view. Recent studies have also been made regarding the cobalt content in leather and its role in contact allergy. It is well-known that cobalt may be used in leather production as a pigment and also sometimes as a drying agent. In 2013, a case report was published regarding a patient with chronic contact dermatitis [65]. Investigating possible cobalt exposure, the patient's leather sofa was identified as the only single source of cobalt. This was followed by a larger questionnaire study among dermatitis patients focusing on cobalt allergy and dermatitis caused by leather articles [66]. In the latter, it was shown that there seemed to be a positive association between cobalt allergy and nonoccupational leather articles.

Several research studies have elucidated the release of metals from different types of electronic devices [67–72], with the main focus on nickel. However, in some of these studies, the presence of cobalt has also been studied, mainly through usage of the cobalt spot test [73] and by studying release using artificial sweat solution

[68]. These studies have shown that cobalt is present on the surface of, for example, flip phones and laptop computers [67, 68]. Although the contact time with these items is not always continuous, they may still elicit dermatitis in already sensitized patients. This is troublesome since these types of items have become an ubiquitous commodity in our daily lives.

28.6 Assessment of Skin Exposure

The factors governing skin deposition of metals have been described in more detail in Chap. 6. In short, when the skin comes in contact with a surface containing metals, the result is an immediate transfer of metal ions to the skin [74]. Once the metals have been deposited through such direct contact by touch or by deposition of particles on the skin, or by applying, for example, make-up on the skin, the actual skin dose can be evaluated via the sampling of metals from the skin.

One method that has been much used to evaluate the cobalt skin dose is the acid wipe method [75]. In this method, the skin is sampled by a wipe moistened with a weak dilution of nitric acid, which will not harm the skin. The metal content of the wipe can then be analysed chemically. The benefits of using this method are that the corresponding skin dose (μg/cm^2) will give quantitative information on the amount of metal present on a defined surface area of skin that was sampled, which is important for the development of contact allergy. Acid wipe sampling has mostly been used for studying skin exposure to metals in different occupational settings [56, 76] and also in laboratory studies of experimental deposition of metal on the skin [66, 77].

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Metal Allergy: Copper

29

Simon W. Fage

29.1 Introduction

Copper (cuprum, Cu) is a chemical element with the atomic number 29. It is a soft and malleable metal with a reddish-orange colour. With time, it corrodes to show a green patina. Copper can form a rich variety of compounds, usually with the oxidation states +1 and +2. The simplest compounds of copper are binary, containing only two elements, with the main ones being the oxides, sulfides and halides. As many as 400 different copper alloy compositions are loosely grouped into, for example, copper, high-copper alloys, brasses, bronzes, cupronickel, copper-nickel-zinc (nickel silver), leaded copper and special alloys. Copper is used for various purposes, and aside from cutaneous exposure, the human mucosa is exposed to copper from intrauterine contraceptive devices (IUDs) and dental restorative materials. Although humans are widely exposed to copper on the skin, allergic contact dermatitis caused by copper is infrequently reported, and most reports of immune reactivity to copper involve exposure through the mucosa, implicitly excluding the role of skin contact. Thus, the role of copper as a sensitizer remains controversial.

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29.2 Exposure

Worldwide production of copper is steadily increasing (Fig. 29.1). Copper has a very high thermal and electrical conductivity, and it remains the preferred electrical conductor in electrical wiring [1]. Major applications of copper are thus in electrical wires and electronics, but also in construction, transport and industrial machinery. Mostly copper is used as a pure metal, but, when greater hardness is needed, it is combined with other elements in a variety of alloys to which consumers are widely exposed [2] (Fig. 29.2). Copper constitutes a large proportion of cupronickel coins, which are used worldwide [3–6]. The €2 coins are made of 75% copper, and the other euro coins also contain high levels [3]. Copper is used in door fittings, knobs and taps, and it is also a principal metal used to produce both inexpensive jewellery and carat silver and gold [4, 7]. Thus, in a study determining the composition of 956 inexpensive metallic pieces of jewellery, Hamann et al. [8] found copper to be the most common metal by far. Copper, in concentrations of 5 to almost 100%, is also commonly used in dental applications [9–12]. Copper-containing intrauterine devices (IUDs) are used for reversible contraception, and approximately 5% of British women and 10% of Danish women are exposed to copper this way [13]. The copper used in copper-containing IUDs is quite pure, and, according to the Danish drug adminis-

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Fig. 29.1 Trends in world production of copper

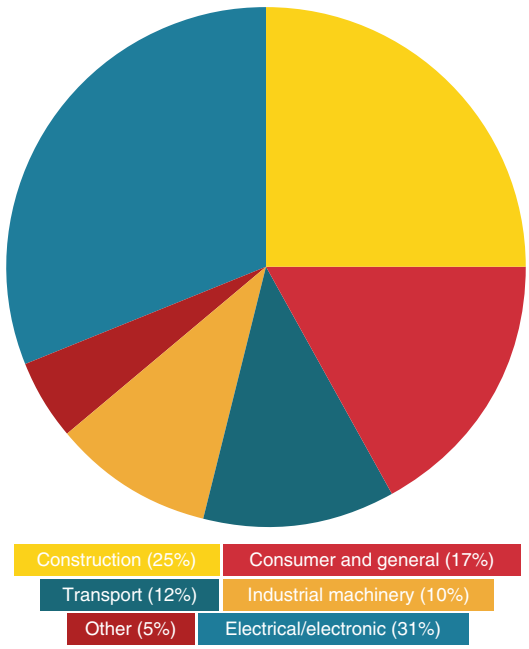

Fig. 29.2 Applications of copper

tration, the rate of copper release is 17–45 µg/day. Notably, the content of nickel is reported to be very low [14, 15]. In the farming industry, copper sulfate is used as a pesticide [16]. In recent years, several studies have investigated the efficacy of copper and copper surfaces to destroy a wide range of bacteria (including resistant strains such as MRSA), viruses and fungi, with good results [17–23]. Antimicrobial copper alloy products are thus being adopted in healthcare facilities [24], and copper alloy handrails are installed in the subway transit system in Santiago, Chile [25, 26].

29.3 Ion Release and Deposition

In a migration study [27], coins (95% copper), copper-coated paper clips (0.005%) and copper thread (99.99%) were immersed in artificial sweat for 24 h. A final concentration of only 0.01% copper was found in the solution. The authors concluded that the concentration of copper was too low to elicit allergic contact dermatitis or that only highly sensitized individuals would react. Likewise, findings from a study by Stoffolani et al. [9], who investigated the release of copper from orthodontic appliances in solutions made with different pH values to imitate the oral environment, suggest that the quantities of copper released should be of no clinical concern. Nevertheless, free copper is released from gold alloys into synthetic sweat [4], and when Lidén et al. [28] investigated metal release in synthetic sweat from 13 different gold-containing jewellery alloys, copper, but not gold, was released from all of them. Hence, from gold-plated brass, as much as 290 µg copper/cm^2/week was released. For the other 12 jewellery alloys, an average release of 0.33 µg copper/cm^2/week (0.05–0.72) was found. It could be important to consider these findings in cases of contact dermatitis caused by jewellery made of gold alloys, as the presence of a precious metal enhances the ionization of non-precious metals [28]. Regarding coins, it has been claimed that the duration of skin contact is too short to cause metal release and to elicit dermatitis. It is, however, well known by dermatologists and by allergic patients that hand eczema in cashiers and other professionals handling coins may be caused or aggravated by the release of metal. Nickel [6] and also copper have been shown to be released onto the skin from everyday handling of coins [29]. Thus, a comparison of coins used in France indicated that the introduction of the euro has led to a fourfold reduction in contamination by nickel but a 45% increase in contamination by copper [29].

29.4 The Sensitizing Potential of Copper

According to the predictive guinea pig maximization test (GPMT) and the local lymph node assay (LLNA), copper has a relatively low sensitization potential [4, 9] (Table 29.1). The GPMT measures the allergic reaction, if any, on the test animals after initial intradermal exposure to a test material along with an adjuvant and, a short time later, exposure to a lower concentration of the test material. The LLNA relies on measurement of events induced during the induction phase of skin sensitization, specifically lymphocyte proliferation in the draining lymph nodes. Skin sensitizers are defined as chemicals that induce a threefold or greater increase in lymphocyte proliferation as compared with controls. This is referred to as a stimulation index (SI) of >3. The lowest concentration to yield an SI of >3 is estimated as the so-called EC3. Fukuyama et al. [30] found the EC3 value to be 1.69% of copper oxide in acetone/olive oil or dimethylsulfoxide. Both Basketter et al. [31], in 1996, and the Interagency Coordinating Committee on the Validation of Alternative Methods [32], in 2001, have reviewed experimental studies using the LLNA and different guinea pig tests. Regarding copper, both found a tendency towards positive results with the LLNA and negative results with guinea pig tests. Thus, in accordance with the listed LLNA results, copper seems to have a low sensitizing potential under experimental conditions. The method applied should of course be considered, and it is unclear to what degree these levels are relevant in humans.

29.5 Epidemiological Studies

A retrospective analysis of 2660 routine patch test results found 94 patients (3.53%) with a positive reaction to copper sulfate. Hence, 2% copper sulfate was the eighth most frequent metal to give a positive result on the list of 34 routinely tested metal allergens [4]. In another retrospective study of 931 patients patch tested between 1990 and 2009, copper was the third most frequent metal to give a positive result in those patch tested after year 2000 [38]. On the basis of 33 published studies (Tables 29.2, 29.3, 29.4 and 29.5), a total of 13.765 subjects (healthy controls, dental patients and dermatitis patients) have been patch tested with copper, mostly as copper sulfate in different vehicles and concentrations. Considering only the 265 healthy subjects, none tested positive. Considering only subjects with presumed related symptoms and/or suspected exposure, a weighted average of 3.8% tested positive. Three groups are of particular interest: (1) patients with dermatitis (Table 29.2), (2) subjects who have had dental work performed (Table 29.3), and (3) dental technicians and dentists (Table 29.4), as the latter frequently have dermatitis of the hands and handle copper-containing alloys [39]. When epidemiological data on these groups were analysed, the weighted average prevalence rates of patch test reactivity to copper were 5.4% in dermatitis patients, 0.2% in patients with dental prostheses and 3.2% in dental workers and technicians. When considering only the larger studies with >100 subjects, the weighted average prevalence rates of patch test reactivity to copper were 4.8% in dermatitis patients and 0.2% in patients with dental prostheses. Few studies have performed follow-up patch testing with copper: upon retesting of 26 patients with a previous positive reaction to copper, Wöhrl et al. [4] found only ten patients (38%) to have a positive test reaction. However, in a previous study, Wöhrl et al. [40] found 13 of 14 patients to have positive test results upon retesting.

29.6 Patch Testing

Copper sulfate is included in many metal patch test series, but there is no consensus regarding the concentration of copper and which vehicle to use. With a relatively weak sensitizer as copper, the general challenge with reproducibility of metal patch testing is indeed a concern, and other aspects should be taken into consideration as well. For example, copper patch test materials can contain nickel as an impurity, and highly sensitized subjects can react to very low concentrations

Table 29.1 The sensitizing potential of copper: summary of results of the guinea pig maximization test and the local lymph node assay

				LLNA				GMPT			
Author	Year	Country	Compound	Conc.	Vehicle	No.	SI	Challenge conc.	Vehicle	No.	Interpretation
Boman et al. [33]	1979	Sweden	Copper sulfate					0.1, 0.5, 1.0%	Pet.	20	**Sensitizer**
Karlberg et al. [34]	1983	Sweden	Copper sulfate					0.1, 0.5, 1.0%	Pet.	57	Non-sensitizer/weak
Basketter et al. [35]	1992	UK	Copper chloride	0.5%	DMSO	4	**8.1**	0.25%	NaCl	NA	Non-sensitizer
			Copper chloride	2.5%	DMSO	4	**13.8**				
			Copper chloride	5.0%	DMSO	4	**13.6**				
Ikarashi et al. [36]	1992	Japan	Copper sulfate	10.0%	Ethanol	3	2.67				
Yamano et al. [37]	2006	Japan	Copper naphth.	0.3%	[a]	4	~1	0.50%	Pet.	5	Non-sensitizer
			Copper naphth.	1.0%	[a]	4	~1				
			Copper naphth.	3.0%	[a]	4	**~5**				
			Copper naphth.	10.0%	[a]	4	**~9**				
			Copper chloride					1.00%	Ethenol	5	Non-sensitizer
Fukuyama et al. [30]	2008	Japan	Copper oxide	0.3, 1, 3%	[b]	30					
			Copper oxide	0.3%	AOO	5	1.2				
			Copper oxide	1.0%	AOO	5	1.25				
			Copper oxide	3.0%	AOO	5	2.5				
			Copper oxide	0.3%	DMSO	5	1.74				
			Copper oxide	1.0%	DMSO	5	2.04				
			Copper oxide	3.0%	DMSO	5	**4.83**				

[a]Petroleum ether and olive oil
[b]Acetone/olive oil (AOO) or dimethylsulfoxide (DMSO)
Bold – SI > 3

Table 29.2 Patch test studies: patients with dermatitis, metal exposure and/or a previous positive patch test to a metal

Author	Country	Year	Patient group	Vehicle	Concentration	Readings	No.	Pos. (no.)	Pos. (%)	+ sens. to Ni
Epstein S [41]	US	1955	Metal sensitized	NR	10.0%	NR	32	14	44	12 (86%)
Dhir et al. [42]	India	1977	CD, furniture polishers	Aq.	5.0%	NR	10	10	100	NR
Karlberg et al. [34]	Sweden	1983	Eczema	Pet.	2.0%	NR	1190	13	1	
Walton et al. [43]	England	1983	Eczema	Pet.	5.0%	48, 96 h	354	6	1.7	6 (100%)
	England	1983	Pos. to copper initially	Pet.	0.25%	48, 96 h	6	6	100	
	England	1983	Pos. to copper initially	Pet.	0.50%	48, 96 h	6	6	100	
	England	1983	Pos. to copper initially	Pet.	1.00%	48, 96 h	6	6	100	
Lisi et al. [44]	Italy	1987	CD and/or agricultural occupation	Pet.	1.0%	48, 72 h	564	4	0.7	NR
Romaguera et al. [45]	Spain	1988	CD from metal	NR	100% copper	48, 96 h	964	140	14	NR
	Spain	1988	CD from metal	NR	70% brass	49, 96 h	964	76	8	NR
	Spain	1988	CD from metal	NR	80% bronze	50, 96 h	964	46	5	NR
van Joost et al. [46]	The Netherlands	1988	Sensitized to nickel	Aq.	5.0%	48, 72 h	11	0	0	
	The Netherlands	1988	Sensitized to nickel, CD	Aq.	5.00%	48, 72 h	2	2	100	2 (100%)
Santucci et al. [47]	Italy	1993	Sensitized to nickel	Aq.	2.50%	48 h	120	0	0	
Rademaker et al. [16]	New Zealand	1998	Farmers, dermatitis	NR	2.0%	48, 96–120 h	46	5	11	NR

(continued)

Table 29.2 (continued)

Author	Country	Year	Patient group	Vehicle	Concentration	Readings	No.	Pos. (no.)	Pos. (%)	+ sens. to Ni
Wöhrl et al. [4]	Austria	2001	Dermatitis	Pet.	2%, 0.6% and 0.2%	72 h	2660	94	3.5	(64%)
	Austria	2001	Tested pos. to copper	Pet.	5% and copper disc	48, 72 h	26	10	38	8 (80%)
	Austria	2001	Tested pos. to copper	Pet.	2% and below	48, 72 h	26	2	7.7	2 (100%)
	Austria	2002	Tested pos. to copper	Aq.	1.00%	48, 72 h	26	0	0	
Lisi et al. [48]	Italy	2003	Sensitized to cobalt	Aq.	1.0%	48, 96 h	60	1	1.7	1 (100%)

CD contact dermatitis, *NR* not reported, *Pet.* petrolatum, *Aq.* aqueous
The compound used is copper sulfate unless indicated otherwise

Table 29.3 Patch test studies: patients with a dental implant with and without symptoms

Author	Country	Year	Patient group	Vehicle	Conc.	Readings	No.	Pos. (no.)	Pos. (%)
Stenman and Bergman [49]	Sweden	1989	Dental materials and symptoms	NR	1%	NR	151	0	0
Vilaplana et al. [50]	Spain	1994	Dental materials and symptoms	Pet.	1%	NR	66	1	1.5
Marcusson [51]	Sweden	1996	Dental materials and symptoms	Aq.	2%	96 h	397	0	0
Laine et al. [52]	Finland	1997	Dental materials, oral lichenoid lesions	NR	NR	48, 96 h	23	0	0
Koch and Bahmer [53]	Germany	1999	Dental materials, oral lichenoid lesions	Aq.	1%	3, 10, 17d***	19	0	0
Vilaplana and Romaguera [12]	Spain	2000	Dental prostheses	Pet.	1%	NR	520	3	0.6
Kanerva et al. [54]	Finland	2001	Retrospec., patch tested dental series	NR	NA	48 h, 96–144 h	2611	6	0.2
Ditrichova et al. [55]	Czech Repub.	2007	Oral lichenoid lesions	Pet.	2%	48, 96, 168 h	25	0	0

NR not reported, *Pet.* petrolatum, *Aq.* aqueous
The compound used is copper sulfate

Table 29.4 Patch test studies on dental personnel

Author	Country	Year	Patient group	Vehicle	Conc.	Readings	No.	Pos. (no.)	Pos. (%)
Oshima et al. [56]	Japan	1991	Instructors at dental school	NR	NR	48, 72 h	31	0	0
Kawahara et al. [57]	Japan	1993	Students at dental school	Aq.	1%	48, 72 h	12	1	8.3
Kanerva et al. [58]	Finland	1993	Hand dermatitis, dental workers	Aq.	2%	NR	4	0	0
Uveges et al. [59]	USA	1995	Dental personnel, CD	NR	1.00%	48, 96 h	27	0	0
Lee et al. [39]	Korea	2001	Dental technicians	NR	NR	72 h	49	3	6.1

CD contact dermatitis, *NR* not reported, *Aq.* aqueous
The compound used is copper sulfate

of nickel [11]. Thus, it has been speculated that false-positive patch test reactions to copper could result from traces of nickel in the patch test used. To address these speculations, Wöhrl et al. [4] determined the content of nickel in copper sulfate and copper metal foil samples by graphite furnace atomic absorption spectrometry. Pure copper sulfate contained <0.0002% nickel, 5% copper sulfate pet. contained <0.00001%, and pure metallic copper foil contained <0.0005%

Table 29.5 Patch test studies, unclassified

Author	Country	Year	Patient group	Vehicle	Concentration	Readings	No.	Pos. (no.)	Pos. (%)	+ Sens. to Ni
Dhir et al. [42]	India	1977	Healthy controls	Aq.	5.00%	NR	15	0	0	NR
Dry et al. [60]	USA	1978	Copper IUD	NR	5.00%	48 h	69	1	1.4	NR
	USA	1978	No copper IUD	NR	5.00%	48 h	50	0	0	
Jouppila et al. [61]	Finland	1979	Copper IUD, skin rash	Pet.	5.00%	72 h	10	0	0	
Frentz and Teilum [14]	Denmark	1980	Copper IUD, skin rash	Pet.	2.5 and 5%	NR	7	0	0	
Romaguera and Grimalt [62]	Spain	1981	Copper IUD and skin symptoms	Aq.	2.00%	NR	4	4	100	1 (25%)
Romaguera et al. [45]	Spain	1988	Healthy controls	NR	100, 70, 80%	48, 96 h	200	0	0	NR
Motolese et al. [63]	Italy	1993	Enamellers and decorators	Pet.	5% (red copper oxide)	72 h	190	1	0.5	NR
Santucci et al. [64]	Italy	1996	Retrospective, patch tested	Pet.	5.00%	48 h	1000	2	0.2	0 (0%)
Nakada et al. [65]	Japan	1997	Ear piercing	Aq.	2.00%	72 h	107	9	8.4	NR
	Japan	1997	No ear piercing	Aq.	2.00%	72 h	270	11	4.1	NR
Wöhrl et al. [40]	Austria	2001	Sensitized to copper	Pet.	5.00%	72 h	14	13	93	NR
Nonaka et al. [38]	Japan	2011	Retrospec., half with CD	Aq.	2.00%	72 h	381	26	6.8	NR

CD contact dermatitis, *IUD* intrauterine contraceptive device, *NR* not reported, *Pet.* petrolatum, *Aq.* aqueous
The compound used is copper sulfate unless indicated otherwise

nickel [4]. Other studies have found analytical-grade copper sulfate to contain up to 0.002% nickel. High-purity copper wire in IUDs, which is also used for skin testing, contains 0.0003% nickel [34]. These concentrations of nickel are far lower than those that are normally expected to cause a positive result in patch testing. Also as a response to speculations about false-positive results resulting from impurities, Walton [66] patch tested 18 nickel allergic patients with previous patch test reactions to 5% copper sulfate and 4 patients with patch test reactions to copper alone. All tests with 0.01% nickel sulfate gave negative results, thus demonstrating that the previous positive reactions to copper were likely not due to impurities with nickel.

With regard to the concentration of copper, 1–5% copper sulfate is most often used in patch testing. Wöhrl et al. [4] suggested that concentrations of <5% in pet. and aq. may not be sensitive enough to detect all copper hypersensitivities. The ICDRG recommends application of 1% copper sulfate in aq. or pet., or an occluded copper disc, for a period of 2–4 days for the verification of copper hypersensitivity [11]. When the epidemiological studies were summarized with regard to the concentration used, a weighted average of 2.6% of subjects reacted to a concentration of 5%, and a weighted average of 2.8% reacted to a concentration of ≤2.5% (all data not shown). Many cases with a positive reaction to 5% copper sulfate pet. have been classified as irritant rather than allergic [11]. Hence, Walton [43] patch tested 354 dermatitis patients with copper sulfate 5% pet. and lower concentrations, which, according to the author, did not cause any irritant reactions. Patch testing with ≥10% did, however, cause irritant reactions. When a ≥5% solution has been used, given the potential risk of false-positive results caused by irritation, the performance of a serial dilution test has been recommended. According to the presented data, this does not seem to be an issue of great importance.

With regard to systemic exposure in dental patients and patients with a copper-containing IUD, it is relevant to consider whether negative patch test results and negative intradermal test results can definitively rule out internal provocation as the cause of a skin eruption. This is dependent on the route of administration, the various possible proteins that can render the metal a true antigen and the different concentrations of the antigen at the site of application [14].

29.7 Immunological Reactivity

Although resistant to corrosion, copper can be converted to diffusible forms able to penetrate biological membranes in a physiological environment [11] and can, like other transition metals, act as a hapten [9, 11, 67]. Partially depending on the type of exposure, copper is one of several metals that has been reported to induce more than one type of hypersensitivity reaction. Thus, immediate-type and delayed-type cutaneous hypersensitivity, immunological contact urticaria, systemic allergic reactions, contact stomatitis and respiratory hypersensitivity have been reported. A dual immune response, e.g. the concurrent occurrence of immediate-type and delayed-type hypersensitivity reactions, has also been described [62, 68–76].

Copper has many chemical similarities with nickel: they are located next to each other in the periodic table, they are both used in many alloys, they can be bivalent as ions and are highly protein-reactive, and they have both been shown to react specifically with the nucleophilic imidazole nitrogen of the histidine residue in the major histocompatibility complex (MHC)-bound peptide or with the MHC molecule itself [77–79]. Additionally, like nickel, copper prefers square planar arrangements of coordination complexes [80], and filaggrin, an epidermal protein, has shown a strong capacity to bind to both nickel and copper in an experimental study ([81], unpublished data). Of note, in a study by Pistoor et al. [67], the maximal stimulatory concentration of copper needed for maximal T lymphocyte clone proliferation was tenfold lower compared to nickel.

The most frequent metal hypersensitivity response is T cell-mediated, which is initiated by an innate immune response. Notably, the initial

innate inflammatory immune response seems to be a prerequisite and very important in both the sensitization and elicitation phases. A particular feature of contact allergens is their irritancy or adjuvanticity, hence their ability to enable innate immune responses. This inherent ability to cause inflammation distinguishes them from conventional protein antigens, which require additional innate signals or the addition of exogenous adjuvants to induce immune responses [82]. The exact mechanisms of induction of the innate immune response by contact allergens are unclear. Contact allergens are able to induce reactive oxygen species (ROS) production in monocytes and dendritic cells in vitro. ROS induce extracellular matrix degradation and are capable of triggering pro-inflammatory cytokine responses via the generation of endogenous toll-like receptor (TLR) ligands [82]. A putative mechanism by which copper and other metals might induce an innate immune response is by direct stimulation of TLRs. Recently, it was discovered that nickel ions are able to directly ligate and trigger TLR4 on dendritic cells [83, 84]. Downstream of the signalling pathway, pro-inflammatory mediators, such as interleukin (IL)-8, IL-1β and tumour necrosis factor-α, are released [83]. These mediators contribute to both rapidly acting innate immune responses and adaptive immunity by driving antigen-induced T cell expansion, cell-mediated immune effector functions and/or recruitment of B cells. The latter leads to antibody generation. Rachmawati et al. [83] investigated the activation of dendritic cells with the surrogate marker IL-8 for nickel, palladium, cobalt, chromium, copper, potassium, zinc and sodium ions. The data showed that cobalt and palladium also had potent monocyte-derived dendritic cell (MoDC)-activating capacities, whereas copper and zinc had low, albeit distinct, MoDC-activating potential. None of the metal-induced responses was affected by clearance of lipopolysaccharide (LPS), a TLR4 agonist; supporting the view that dendritic cell activation is an intrinsic property of the metals. In order to verify that the observed effects were caused by the presence of TLR4 and MD2 (co-receptor for TLRs), the experiments were extended with wild-type non-transfectant HEK293 cells, which do not express TLRs [84]. None of the metals induced detectable IL-8 release, although surprisingly, copper caused a response that was higher than in the TLR4/MD2 transfectant cells. The meaning of this latter result is uncertain, and the authors concluded that, given the adjuvant role of costimulatory danger signals, the development of contact allergies to the metals may be facilitated by signals from direct TLR4 ligation.

29.8 Cross-Reactivity with Nickel

Concomitant sensitivity to several metals is common [80, 83]. With a strong statistical association, a high incidence of nickel sensitization in copper-sensitive subjects has been found [4]. Furthermore, in nickel-sensitive subjects, the simultaneous application of copper and nickel sulfate to the same test site significantly increased the patch test reaction as compared with nickel alone [47]. Cross-reactivity of specific T cell clones, originally proposed by Epstein in 1955, is a possible explanation for this [41]. To some extent, the cross-reactivity model contradicts the claim that many copper patch test reactions are irritants in nature, as irritant reactions should not generally be associated with hypersensitivity to nickel but should be equally distributed between subjects. Several experiments have shown that nickel-specific T cell clones do indeed cross-react with some transition metals, e.g. copper and palladium, presented by identical MHC class II molecules [67, 80]. Cross-reactivity with copper and palladium might be favoured by their bivalency, their location next to nickel in the periodic table [67] and by the similar geometries of their coordination complexes [80].

29.9 Case Reports

Cases of contact dermatitis caused by jewellery containing copper in different alloys have been reported repeatedly [46, 85]. A case report [86] describes a 22-year-old house wife who presented with a 3-month history of dermatitis spo-

radically affecting the palmar surface and the dorsal surface of the distal phalanges of all her fingers. The history suggested nickel allergy as the cause, and patch testing with 5% nickel sulfate in pet. was positive. On examination of the patient's coin purse, a marked bluish-green discolouration was seen on the inner surface, and a small square of this fabric gave a 3+ reaction when applied to her back for 72 h. Because the staining of the lining of her coin purse suggested contamination mainly with copper rather than nickel, she was patch tested with 5% copper sulfate in aq., which gave a 3+ reaction after 72 h. Preventive measures to avoid metal contact led to marked symptom relief. Another case report describes a 39-year-old man [3] with no history of atopy, who developed dermatitis on the fingertips, both upper eyelids and the outer canthi after working in a bingo hall for 12 months handling €2 coins. He described considerable improvement at weekends and during vacations. Standard metal patch testing showed a positive reaction only to copper sulfate 5% pet. Just recently, a case of copper allergy in a child has been reported [87]. The 5-year-old patient had a 2-year history of fingertip dermatitis mostly affecting the first three digits of the right hand and a history with improvement when being away from home and school. Patch tests gave a strong positive reaction to copper and no reaction to nickel. A detailed history showed that the patient was playing with 1p and 2p coins containing copper and die-cast model cars made from zinc, aluminium, magnesium and copper. Upon removing the model cars and a reduction in handling coins, the mother reported improvement over a 6-month period.

The clinical role of copper release is suggested in a case report of a 56-year-old woman [88] presenting with a 5-year history of painful lichenoid lesions on the left buccal mucosa and the left side of the tongue, which was adjacent to a dental metal prosthesis. There were no lesions outside the oral cavity. A biopsy showed lichen planus, and treatment with triamcinolone acetonide had no effect. Patch testing with a baseline series and other relevant potential allergens gave positive results only with 2% copper sulfate. The dental prosthesis contained copper, and, after the prosthesis had been changed to one without copper, there was almost immediate relief of symptoms, and the lichenoid enanthem disappeared. Similar reactions to dental materials, including cases leading to urticaria and porphyria, have been reported [85, 88–90].

Eczematous eruptions and even urticaria have been attributed to the copper-containing IUD. All patients have had a positive patch test reaction to copper, and, in the majority of cases, there was complete resolution shortly after removal of the IUD [68, 69, 91, 92]. In one case report [68], a 26-year-old woman developed dermatitis on her arms, which gradually generalized. Her medical history was unremarkable; however, she recalled having a copper-containing IUD inserted two weeks before the onset of her symptoms. The IUD was removed, and patch testing showed reactivity to 5% copper sulfate. The symptoms completely cleared after removal of the IUD. Zabel et al. and Hausen and Hohlbaum [93] investigated several women having cutaneous symptoms after using a copper-containing IUD. The prevalence of positive reactions to copper was relatively low, but removal of the IUD caused remission of the symptoms in all women.

29.10 Conclusion

Copper seems to be a weak sensitizer as compared with other metal compounds. However, in select cases, copper can result in clinically relevant allergic reactions. It is currently unclear to what degree nickel-allergic individuals may react to copper released from metal alloys, due to cross-reactivity.

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Metal Allergy: Gold

30

Cecilia Svedman and Magnus Bruze

30.1 Exposure and Human Use of Gold

Gold (Au; latin: aurum) is a noble metal with the atomic number 79. It is soft, ductile and with a low melting point. Gold is abundant in low concentrations in the environment mostly in metallic form, but can also be found as gold telluride [1]. It can occur in two oxidation states (+1 and +3).

Due to its use in jewellery, gold is a metal that a large proportion of the population, especially females, are in skin contact with often more or less continuously. In jewellery and ornamentation, it has been used since antiquity. When used in jewellery, the fineness of gold is defined with the karat, equal to 1/24 part, pure gold thus being 24 karat. Gold in jewellery can therefore contain not only gold but also other metals such as copper, zinc and tin. Interestingly, increased copper content seems to increase gold dissolution; thus, lower karat gold may release more gold, which may possibly also be of importance as to whether there will be a contact allergic reaction [2]. White gold is a gold-based alloy with multiple constituents giving rise to the colour, and the alloys may contain palladium, nickel, zinc and cadmium [3]. Gold has also been used in electronics.

Gold is also known as a medical agent in the form of gold dust or flakes (used in China since 2500 BC). In modern times, gold salts have been given intramuscularly or orally to treat inflammatory disease such as arthritis [4, 5] for more than 70 years. The metal is sometimes considered a health-improving substance [6, 7]. The metal has also been used in medicine due to its ability to prevent adhesion of microorganisms and, additionally, has been used in drug delivery chips [8, 9]. For dental constructions, gold has been used for decades in high noble or noble alloys due to its corrosion and tarnish resistance and relatively good biocompatibility. Its use has however decreased due to the dramatic increase in the price of gold and since base metal alloys have been introduced [10, 11]. Gold as a pure metal is not usually used since it lacks sufficient physical and mechanical resistance against masticatory forces and cannot bond to porcelain; therefore, it is alloyed with other metals [11, 12]. Gold has been and is still sometimes used in other implants [13–16].

This versatility in the uses of gold is due to the metal's characteristics of being soft and easy to form or cast. Gold has been considered inert and resistant to corrosion because it does not combine with oxygen or other substances in the

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atmosphere. When the metal first appeared as a possible contact allergen, there was discussion as to whether metal release was possible at all [17–21]. In several studies, however, it has been shown that gold is released in solutions of increasing pH or those containing amino acids with thiol groups. Release has, for example, been found in solutions containing cysteine and glutathione. Thus it can be concluded that metal release does exist and differs depending on the alloy and extraction media [22, 23].

30.2 The Patch Test Screening Allergen and Patch Test Reaction

In the 1960s, Kligman found gold chloride to be a strong sensitizer in the human maximization test [24]. Contact allergy has been demonstrated by patch testing with the metal as such [25], which may however yield false negative results [26]; thus, initially a variety of gold salts were used [27–32]. In the late 1980s, gold sodium thiosulphate (GSTS) in pet at 0.5% wt/wt was reported to be a good screening preparation, followed by GSTS at 2.0% in the mid-1990s [33]. This substance is also commercially available in concentrations of 0.25% pet and 75 μg/cm2. Apart from GSTS, potassium dicyanoaurate (I) is a patch test substance that has been used clinically in 0.1% aq and 0.002% pet. Studies have been performed arguing that several gold salts and also different dilutions of each salt might be needed in order to capture all gold-positive patients [34, 35]. The current experience of testing with GSTS at 2%, however, does not seem to warrant a more routine use of other patch test substances.

The optimal patch test dose has also been discussed and it has been suggested that, since patients may turn positive to lower concentrations, several concentration gradations should be used [34, 35]. However, recent research with a dilution series of GSTS in previously established gold-allergic patients rather suggests that there may be greater variability in patch test reactivity as the concentration decreases [36]. Thus, presumably GSTS 2% pet is, until further research has proven otherwise, the optimal test concentration [13].

Positive patch test reactions may appear late, and readings should therefore be performed at Day 7 [37–39]. With late-appearing test reactions, active sensitization is sometimes suspected. This can be evaluated by retesting the patient with GSTS: if a positive reaction then promptly occurs on day three, this indicates active sensitization [39].

If the patch test reaction is doubtful and there is a high clinical suspicion for allergic contact dermatitis, the patient can be retested at 5% pet. A positive patch test reaction may also be long-lasting, sometimes persisting for several months and occasionally forming a nodular reaction. To prevent or minimize this, a strong positive reaction can be treated with a potent corticosteroid cream under occlusion for a few days.

30.3 Indications for Patch Testing to Gold

The inclusion of gold in the baseline series is controversial. Gold is not included in the European Baseline series, and neither is it in the standard allergen series of the North American Contact Dermatitis Group (NACDG). However, the American Contact Dermatitis Society Core Allergen Series Committee included it in Core Panel IV (gold sodium thiosulfate 2% pet), and it has recently been added to the TRUE test (75 μg/cm^2 of gold sodium thiosulfate) (Mekos Laboratories A/S, Hilleröd, Denmark) [35]. In the Chemotechnique Diagnostics series, it is included within the international comprehensive baseline series at 0.5% pet, in the metal series at 0.5% pet and 2% pet, and in the dental series at 2% pet. The general recommendation is that, since patch testing with gold may be difficult to read, may give rise to persistent reactions, and since clinical relevance is often difficult to prove [39, 40], the substance should primarily be included in dental series, metal series, and of course be considered in targeted testing.

30.4 Contact Allergy to Gold

Contact allergy to metals is common. When acting as a contact allergen, the metal is in an ionized form and normally has to be protein-reactive to become immunogenic and evoke an immune response. In the skin, the metal forms covalent bonds with cellular and matrix proteins, especially those containing cysteine and histidine residues, creating epitopes that can be recognized by T-cells. To become fully immunogenic, the free metal ion should also provide innate immune danger signals to the antigen-presenting cells, leading to cytokine production and dendritic cell maturation and mobilization to the draining lymph node [41]. In the lymph node, the metal-containing complex is presented to the T-cells as seen with organic haptens.

It has been shown that gold is released from objects when in close contact with the skin, especially over a prolonged period of time. The amount of gold released depends on the local environment and whether the gold is within an alloy [23, 42]. When interpreting contact allergy frequencies with regard to gold, it is as always important to consider the exposed population, and at what dose the individuals have been patch tested. Therefore, frequencies in studies vary [35]. In Malmö, the patch test substance used has since the early 1990s been GSTS at 2% pet, and the allergen has been in the baseline series (i.e., all consecutive dermatitis patients seen in the department have been patch tested). Patch testing personnel are trained at regular intervals to keep the dose at 20 mg, thus minimizing the risk of irritative or doubtful reactions due to inaccuracy in the patch test dose [43]. In a Swedish retrospective analysis from Malmö [44] based on all patch tested patients 1995–2014 (13,106 patients, ♀:♂ 8191:4915, mean age 48 years), 1883 (♀:♂ 1472:411) were positive to gold upon patch testing. This frequency can be compared to the frequency of 18.4% reported from the Mayo Clinic (2000–2009) when the patch test substance was 0.5% pet GSTS [34]. The NACDG with the same patch test preparation reported a frequency of 8.7% in the years 2003–2004 [45]. Both publications also reported a decrease in frequency over time. This was found also in the Swedish study [44], there interpreted as being due to a reduction in exposure to dental gold.

There are few data on contact allergy to gold in the population at large. At a plant manufacturing binders for paints, all employees underwent patch testing with a test series containing GSTS at 2.0% in pet. Contact allergy was demonstrated in 10.3% of the employees, who were production, laboratory and office workers [46]. Of note, this number is similar to that found in dermatitis patients, where frequencies between 5 and 10% are usually reported [40, 47–50]. In an elderly population investigated after being treated with percutaneous coronary intervention and stented with a stainless steel stent (not containing any gold) (314 patients, ♀:♂ 68:246, mean age 67.4), 28.3% (♀:♂ 36.8%:26%) had a contact allergy to gold [13]. A multivariate model for the association between stent type and contact allergy to gold found a correlation between dental gold and contact allergy to gold, which may in part explain the higher value [13].

30.5 Clinical Relevance

Although contact allergy to gold is frequent, with patch test frequencies sometimes as high as >30% [35], clinical relevance is often difficult to prove. Contact allergy to gold is associated with age, female sex, gold dental restorations, facial dermatitis and ear piercing [49, 51, 52]. In a double-blinded study where 60 individuals with gold contact allergy were instructed to wear for 8 weeks either gold-coated (n = 30) or titanium nitride (n = 30) earrings, there was a significantly higher number that developed ear lobe reactions to the gold-coated earrings (12 vs 5) [52]. In ear lobe dermatitis caused by gold, scanning electron microscopy and X-ray microanalysis have shown small dense fragments containing gold [53].

On the other hand, a patient with a clear positive reaction may very well have no clinical symptoms when wearing gold jewellery. In a study where patients with no known contact allergy to gold used gold plates in close contact with the skin for a maximum of 168 hours, metal

release could be found in 7 of 9 individuals, as well as an increase of metals on skin when the provocation time was prolonged [23]. On the skin, the metal release from gold discs varied from 0 to 0.0178 μg/5 discs with a total disc surface of 15.7 cm^2 (mean value 0.0042 μg/5 discs or 0.00027 μg/cm^2) occluded to the skin. This corresponds to a release of about 100,000 times less than the content of gold in a Finn patch test chamber with GSTS at 2% pet (area of 0.5 cm^2, equivalent to a surface concentration of about 30 μg GSTS cm^2 [23]).

Clear clinical relevance has, however, been demonstrated when studying implants made of gold. Studies have shown clinical relevance in eyelid dermatitis caused by gold medical implants in the upper eyelid [14]. Also, localized symptoms from the oral mucosa can be seen when gold is used in dental implants [47, 53–55].

30.6 Oral Lesions and Contact Allergy to Gold

Patients with oral lesions in the form of oral lichen planus and oral lichenoid lesions have been found to have a higher frequency of contact allergy to gold [55, 56]. Dental material can cause oral lichenoid reactions (OLR) and allergic reactions [57]. The most studied mucosal conditions related to contact allergy are oral lichen planus and oral lichenoid reactions, but controlled clinical trials have been difficult to achieve [58]. Some case reports support an association between a contact allergy to gold and oral lesions (particularly OLR) and report subsequent healing when gold restorations are removed [59–61]. Controlled trials have confirmed that there is a high frequency of contact allergy to gold in patients with oral lichen planus, that sensitization is highly dependent on the presence of dental gold, and that the number of dental gold surfaces is decisive for developing contact allergy [62–64]. Studies have also shown that gold release from dental alloys seems stable over time when the metal is within the oral cavity [65]. The concentration of gold in blood (B-Au) also reflects the presence of dental gold, and patients with contact allergy to gold have been shown to have a numerically higher B-Au than patients without [65]. Thus, the total exposure to gold seems to be of importance.

Clinical work with patients with gold contact allergy indicates that individual patients can tolerate the allergen to a varying degree and, when an individual threshold has been reached, a clinical reaction will ensue, most likely in close proximity to the culprit material. As gold has also been found in the blood, the clinical presentation can differ. The present body of literature justifies the conclusion that, in patients with OLR and contact allergy to gold, gold restorations should be used with caution and additional gold restorations should be avoided. However, if there are no clinical indications for removal of the dental gold, this should not be advised.

30.7 Systemic Exposure to Gold

Systemic allergic contact dermatitis occurs when the sensitized individual is exposed to a hapten or cross-reacting substance systemically, i.e. the hapten is transmitted to peripheral sites. The exposure can occur, for example, orally, intravenously or transcutaneously. There are several case reports on the possible systemic effect of gold as a hapten [6, 48, 61]. In patients treated with gold for their rheumatoid arthritis who developed delayed hypersensitivity symptoms, gold-specific T-cells have been isolated [66]. Möller et al. found that intramuscularly administered gold in gold-allergic patients caused flares of previous patch tests, and in some patients morbilliform eruption and fever. Blood samples showed increased levels of C-reactive protein, tumour necrosis factor a, interleukin-1ra, and sTNF-R1 [67–69]. It is well known that patients with gold allergy have a higher blood gold level (B-Au) compared to those non-allergic. Dental gold has been found to be a risk factor for high B-Au [62, 63, 70], and smoking has been shown to be a risk factor for higher concentrations [71, 72]. It has furthermore been shown that patch test reactivity is correlated to the B-Au [73] (Fig. 30.1). Thus, gold as a circulating hapten can

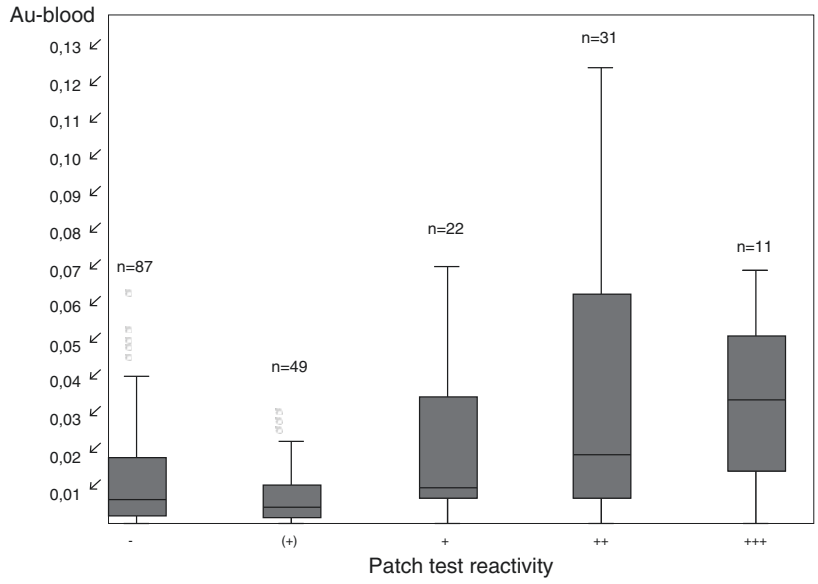

Fig. 30.1 The correlation between concentration of gold in blood (y-axis) and the patch test reactivity (x-axis). The higher the reactivity, the higher the concentration of gold ($p > 0.001$, Spearman's correlation). (Adapted from data from [73])

cause localized and systemic symptoms. It is possible that the circulating hapten may be of importance for whether allergic contact dermatitis will be elicited when in local contact with the hapten.

The importance of gold as a circulating possible hapten has also proven of interest with regard to cardiovascular stents (see Chap. 20). Medical implants are becoming increasingly common, and allergic reactions due to stents and endovascular devices are not fully understood. Bare metal stents used in percutaneous coronary interventions (PCI) to keep the vessel lumen patent in themselves provide a risk of excessive neointimal proliferation [74]. There are several reasons for this, including the possible impact of metal ion release. Bare metal stents will release ions as a result of surface corrosion, and this has been one reason for coating the bare metal stents: among other metals, gold has been used for coating stents in the past [13, 42, 75, 76].

Gold-coated stents have been reported to be associated with a higher frequency of restenosis. In Malmö, a larger retrospective study was performed comparing patients given one of two anatomically identical stent types, where one had been coated with gold. The investigation also included patch tested age and sex-correlated control patients with dermatitis. Multivariate analysis accounting for other risk factors for gold allergy and restenosis showed an association between gold allergy and gold stent placement and, furthermore, an association between gold stent placement, contact allergy to gold, and restenosis [76].

In the Malmö study, it was also found that patients with gold stent placement and gold allergy had higher concentrations of gold in the blood [77]. These findings are interesting in that they also imply that contact allergy can be of importance for the inflammatory response elsewhere than on the skin.

30.8 General Recommendations on Patch Testing with Gold

Recommendations can be summarized as follows:

- Gold should be patch tested as GSTS at 2.0% pet. Patch test readings should be performed twice on day 3 or 4 and on day 7 since late positive reactions are common.
- It is important to perform readings according to the International Contact Dermatitis Research Group classification, as the patch test reaction may be difficult to read (Figs. 30.2 and 30.3).

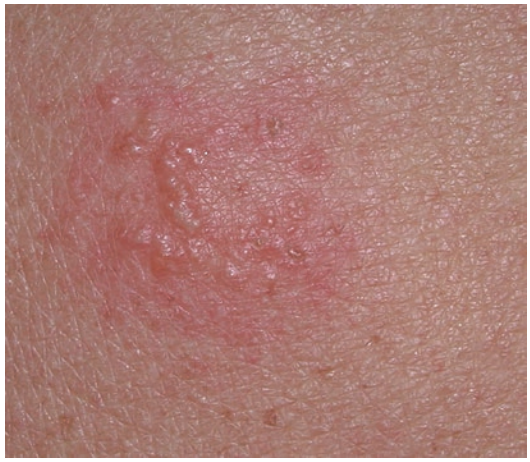

Fig. 30.2 Positive gold reaction (++)

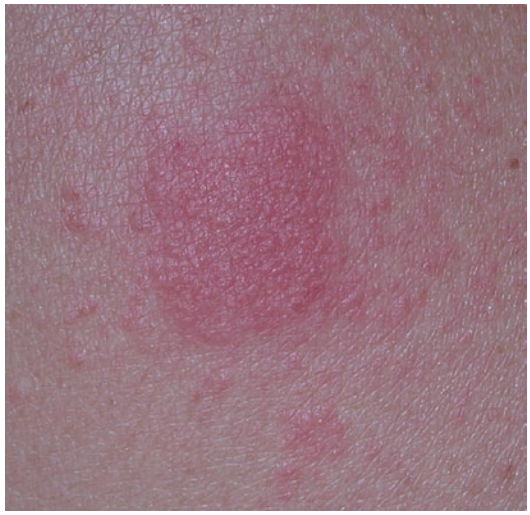

Fig. 30.3 Positive gold reaction (++)

- Patch testing with gold, however frequent the allergy is, still cannot be said to merit incorporation in the baseline series since relevant reactions are not as common as contact allergy. However, the exposure frequency in society has to be evaluated. It remains important to include the allergen in the dental series and metal series.
- Targeted testing, especially when there is known or suspected exposure through dental gold or systemic intake, is of the utmost importance and should particularly be considered in groups where the hapten has previously been found relevant, for example in implant patients.

30.9 Interpretation of Positive Reactions and Patient Recommendations

A contact allergy (i.e. positive patch test reaction) per se is not equivalent to clinical disease and, provided that the patch testing and patch test reading have been accurate, implies that the individual has been sensitized and, if exposed to the hapten again in a sufficient dose, will develop a contact allergic reaction. With regard to gold it is often difficult to find relevance. An individual with a clear positive reaction may have no symptoms whatsoever from gold jewellery or dental restorations containing gold. As has been described, the reasons for this may be multiple: (a) the objects the individual is in contact with do not release sufficient amounts of the metal to elicit a reaction; (b) the contact the individual has with gold objects is so brief that the metal release is not sufficient to elicit a reaction; and/or (c) the total amount of gold exposure is not sufficient to provide circulating haptens that will lower the threshold of reactivity (i.e. the patient has dental gold but the gold release is insufficient to promote a skin reaction to occur with topical exposure to gold).

It is of the utmost importance to ask the patient about possible exposures, including dental restorations, implants, etc., which the individual may be totally unaware of as a source of exposure. If there are dental restorations, the individual should be evaluated for mucosal symptoms in the vicinity of the dental restorations. If the positively patch tested person has no clinical symptoms, there is no reason to recommend any changes. However, the patient should be advised to choose other implant/restoration materials in the future in order to avoid a possible permanent exposure to the hapten. If the reactivity to gold is stronger (+++ reactions), this becomes even more essential.

If there are clinical symptoms localized to an area with a non-permanent source of exposure,

removal of the culprit should be easy. If the patient has symptoms that are not relieved by removing sources of local intermittent exposure, the total exposure of gold must be evaluated. Case reports where dental gold restorations or implants (see above) have been removed suggest that many patients actually improve with this intervention; however, the negative aspects and the feasibility of removal have to be taken into account. If removal is not possible, a trial of corticosteroids may relieve skin or oral symptoms and can be slowly tapered [61, 78], the risk however being that the symptoms may reoccur.

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Metal Allergy: Mercury

31

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31.1 Introduction

In recent decades, mercury has been described as a potent metal sensitizer in humans. Allergic sensitization to mercury is caused most often by a type IV hypersensitivity response, which is a cell-mediated hypersensitivity to cutaneous or mucosally contacted, ingested, or inhaled allergenic molecules of mercury and its chemical compounds.

There has been an intense increase in the worldwide prevalence of mercury allergy. The prevalence of mercury allergy in patients with oral (local), systemic (generalized), and immunotoxic reactions to mercury-containing dental amalgam fillings has increased up to two- and threefold, as compared with controls [1]. Mercury compounds (inorganic as well as organic) are able to induce immune and nonimmune toxic effects, and the two can exist simultaneously. This chapter on mercury allergy is confined to the allergic and/or immunotoxic adverse events that have been reported in association with mercury exposure in humans. Comprehensive reviews of the toxicology of mercury have been reported previously [2–4].

On the basis of these and other emerging data, between the 1980s and 1990s, there was the creation of a subfield of toxicology: immunotoxicology, which is the study of the interactions of mercury with the immune system in humans and/or animals. The four principal immunotoxic effects induced by mercury are immune activation, immunosuppression, autoimmunity, and allergic hypersensitivity [2–5].

In particular, "immune activation" has been defined as the proliferation of innate immune cells (including macrophages, dendritic cells, and granulocytes) that is reflected in high circulating concentrations of proinflammatory cytokines, whereas "immune suppression" has been defined as decreased proliferative activity of immune cells. Allergic diseases and autoimmunity, which are immune system-mediated diseases, have been associated with acute and/or chronic exposure to compounds of mercury in humans and animal models of disease [5].

31.1.1 Chemical Species of Mercury

The metallic element mercury was formerly named "hydrargyrum," hence the chemical symbol Hg. The word "hydrargyrum" is derived from the Latin words "*hydr*" (meaning water) and *argyrum* (meaning silver). In this context, the

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name "hydrargyrum," meaning "liquid silver," originated aptly with Aristotle's observations. The liquid mobile form of mercury (Hg^0) was well known in ancient Greece, and mercury was termed "quicksilver" by the Greek philosopher and scientist Aristotle [6].

The transition metal "quicksilver," or mercury, is a chemical element of the periodic table with atomic number 80. It appears as a silvery-white liquid metal in normal conditions at room temperature. As a pure metal, mercury has low electrical resistance; therefore, it has high electrical conductivity, which may have clinical implications.

31.1.2 History of Human Exposure to Mercury

Since ancient times, humans have been exposed to mercury. Compounds of inorganic mercury occur naturally in the Earth's upper layer. The mineral ore of cinnabar is the most important mercury source, in the form of inorganic mercury sulfide (HgS). Natural degassing from the Earth's mantle, including the lithosphere and hydrosphere, also releases mercury vapor into the atmosphere [4, 6].

The history of mercury amalgam "paste" has now been reconstructed based on estimates of ancient health care. The earliest known exposure to the mercury–copper metal paste "amalgam" in human teeth dates back to around 1500 BC, when ancient Egyptian doctors provided "dental work" for patients presenting with cavities in the teeth. This was probably the first direct evidence of ancient dentistry [6].

Early use of metallic liquid mercury also includes a silver–mercury amalgam described in Chinese medical history. During the Tang dynasty (659 AD), Chinese physicians practiced dental care and introduced a "silver paste" containing silvery-white liquid metallic mercury (Hg^0) as a treatment for dental cavities [7]. Thus, it is likely that "silver–mercury paste" was introduced in East Asia from ancient Chinese health-care workers.

31.1.3 Sources of Human Exposure to Mercury

In the general population, individuals are exposed to mercury (i.e., elemental mercury, inorganic mercury, methyl mercury, and ethyl mercury) mainly through three major sources: mercury dental amalgam fillings, fish intake, and some vaccines [2, 3] (Table 31.1). To substantiate the relevance of mercury exposure from vaccines, thimerosal allergy almost disappeared in Danish adults from the general population following its removal from vaccines [8]. However, according to a 1991 consultation

Table 31.1 Natural and anthropogenic sources of mercury

	Source of mercury	Chemical forms of mercury	References
1	Chloralkali plants	Liquid metallic mercury	[5]
2	Degassing Earth's crust	Mercury (elemental, vapors)	[2, 5]
3	Fluorescent light bulbs	Mercury (elemental, vapors)	[5]
4	Fungicides	Organomercurials	[2, 5]
5	Industry (fur, felt, hat industry)	Mercury nitrate	[5]
6	Incubator	Liquid metallic mercury	[2, 5]
7	Mercury ores	Mercury (elemental), mercury sulfide (HgS)	[2, 5]
8	Mercury-based dental amalgam fillings	Mercury (metallic), mercury (elemental, vapors)	[2, 3, 7]
9	Municipal landfills	Mercury (elemental, vapors)	[2, 5]
10	Munitions industry (detonator)	Mercury fulminate, liquid	[5]
11	Pesticides	Organomercurials	[2, 5]
12	Thermostats	Liquid metallic mercury	[2, 5]
13	Volcanoes	Mercury (elemental, vapors)	[2, 5]
14	Waste incinerator	Mercury (elemental, vapors)	[2, 5]

report by the World Health Organization (WHO), mercury-containing dental amalgam is the principal source of inorganic mercury and mercury vapor for the general population [9].

Mercury vapor (Hg^0) is emitted from mercury amalgam surfaces constantly, and its release increases markedly during mastication due to wear-abrasion [7]. The wear, tear, and corrosion of mercury dental amalgam fillings over long time periods may cause remarkably elevated levels of mercury vapor to be released in the oral cavity and, subsequently, into the bloodstream [1].

Amalgam fillings have been shown to contribute approximately two-thirds of the human body burden of mercury [4, 7]. The World Health Organization considers amalgams to be a major source of mercury for the general population. Mercury levels in the blood, serum, urine, saliva, and scalp hair have been significantly associated with the total number of dental amalgam surfaces [4, 7].

Fish and seafood are not a unique source of methyl mercury for humans. More specifically, organic mercury has been found in saliva, owing to mercury dental tooth fillings. A plausible biochemical explanation involves mercury vapor from dental amalgam being reduced to mercuric mercury and then transformed into mono methyl mercury [CH_3Hg^+] [10, 11].

31.2 Inorganic Mercury

31.2.1 Elemental Mercury (Hg^0)

The most common human exposure is by inhalation due to metallic mercury volatilizing to mercury vapor (Hg^0). As a monoatomic gas (Hg^0), mercury vapor is emitted from mercury-containing dental amalgam surfaces constantly, and its release increases markedly during mastication, due to wear-abrasion, as well as tooth brushing [2, 7]. The mixing compound (liquid metallic mercury and powder matrix alloy) leaks mercury vapor (Hg^0) from dental amalgam over time. Therefore, levels of intraoral mercury vapor may actually approach and exceed occupational health limits [2, 7]. In a cohort of 91 patients with clinically significant adverse reactions to mercury dental amalgam fillings, the mean concentration of intraoral mercury vapor was 25.6 ± 27.8 micrograms Hg per cubic meter (threshold limit value, <3 micrograms Hg per cubic meter) [7, 12]. It is lipid soluble and rapidly diffuses across the alveolar membrane (the diameter of the mercury atom is 0.3 nm), and direct measurements indicate that about 80% of the inhaled mercury vapor is absorbed. Of note, the uptake of mercury vapor can be increased via the gastrointestinal tract. The gas molecules of mercury vapor dissolved in water may easily be absorbed and retained in target tissues, absorption occurring with approximately 60% of a single oral dose. With the available evidence, estimates of the amount of inorganic mercury absorbed daily from mercury amalgam fillings range from 9 to 17 micrograms of Hg per day [2]. The elemental mercury (Hg^0) half-life has been estimated ranging from 58 days in the whole body to 64 days in the kidneys [2]. When attached to sulfhydryl groups (−SH) present in ligands, mercury is able to induce nonspecific forms of cell injury and/or programmed cell death (apoptosis) [4, 5].

31.2.2 Inorganic Mercury Salts (I-Hg)

Inorganic compounds of mercury may exist in monovalent (mercurous mercury) or divalent (mercuric mercury) forms. Mercurous mercury, otherwise known as calomel, is considered the principal chemical salt of mercurous compounds. It was the main constituent of the famous teething powder (mixed calomel/talc) and also the antiseptic cream that caused acrodynia in infants and children. For the most part, routes of exposure to mercurous compounds are oral and dermal [13].

Effects of chronic exposure to mercury-containing skin lightening creams in humans have been reported [4]. In the United States, 3.3% of 549 cosmetic skin lightening products were found to contain high levels of mercury exceeding 1000 ppm [13]. Nephrotoxicity, in the form of nephrotic syndrome, has been reported widely in the clinical literature in women who were receiving such mercury-based creams [14].

31.3 Organic Mercury

Organic mercury is usually grouped into two categories: short-chain alkyl mercurials (methyl mercury and ethyl mercury) represent almost stable organomercurials, while arylmercurials and long-chain organomercurials such as phenyl mercury, methoxyethyl mercury, and mercury-based diuretics represent unstable organomercurials. Methyl mercury is found in fish, primarily large and predatory fish (i.e., swordfish, shark, and tuna) [2, 3]. Thimerosal, ethyl mercury attached to a thiosalicylic moiety, is still used as a preservative in some medications [2].

31.4 Manifestations of Mercury Exposure

31.4.1 Mercury Dental Amalgam-Related Allergy

In the largest retrospective observational case series (1115 persons) conducted among patients with adverse health effects to intraoral metal alloys, we evaluated a cohort of 738 patients with laboratory-confirmed cases of adverse events to mercury dental amalgam tooth fillings. The mean age was 46.9 years, ranging from 10 to 87, with a female to male ratio of 2.5:1 [1, 15, 16]. Before the onset of clinical manifestations, the mean duration of exposure to mercury vapor generated from mercury dental amalgam was 20–25 years [10]. In this cohort, the mean number of mercury-based tooth restorations was calculated at about 4.

The risk of allergic sensitization to mercury, as assessed by positive skin patch testing and/or lymphocyte transformation testing (LTT), was consistent across all subgroups of the study population and appeared to be unrelated to the dose.

In fact, concentrations of total mercury in the whole blood of mercury-allergic patients ($n = 34$) were found to be similar to those of 125 controls (8.8 ± 11.4 μg Hg/L versus 7.1 ± 13.9 μg Hg/L) [1]. The recommended threshold limit value for total mercury in whole blood is <2 micrograms Hg per liter [10]. Above this level (<2 micrograms Hg per liter), studies showed an association with oral and/or systemic disease [1, 10, 17].

As observed with the case of acrodynia and hypersensitivity to mercury, even in patients with mercury-induced nephropathy, the immunotoxic reactions are not related to the size of the dose [5].

With regard to sensitive populations (i.e., school-aged children), even though the possible effects of mercury amalgam fillings must be considered, in our department, we thus far have not encountered one case of allergic reactions and/or true allergic events to mercury dental amalgam in children, but we do acknowledge the possibility.

31.4.2 Oral Lichen Planus and Mercury Sensitization

Oral lichen planus (OLP) is the most common mucocutaneous disorder of middle-aged adults associated with allergic sensitization to mercury-containing amalgam [18], and few treatments are available. OLP occurs in patients with long-term exposure to mercury-containing amalgam fillings (Fig. 31.1), as well as in association with intraoral exposure to gold- and/or palladium-based dental alloys or other metal alloys (i.e., chromium, titanium), forming an intraoral electrical current galvanic couple [19]. These immunoallergic transition metals are released into saliva and then are deposited in oral mucosa, causing allergic sensitization, local cytotoxic injury, and tissue damage due to autoimmunity [19].

It has been demonstrated that metallic mercury, the primary component of mercury dental amalgam, has the capability to induce a contact delayed-type hypersensitivity reaction and trigger an immune response in the affected oral mucosa, resulting in injury of epithelial cells by T lymphocytes and the development of oral lichen planus [19]. Also, there is evidence that the combined presence of mercury allergy and oral electrogalvanism increases the risk for local autoimmune inflammatory process like OLP [20].

Previous studies have suggested that chronic long-standing antigen stimulation to mercury compounds may be causative of OLP. Concurrently, the emission of mercury vapor

from amalgams into the oral cavity results in cytotoxicity of oral mucosal cells.

There is a fine line between a local allergic reaction to mercury and a chemical injury induced from the constant release of elemental mercury (Hg^0) as well as mercury cations (Hg^{2+}). OLP is virtually always attributable to allergic reaction to mercury amalgam alloy, which may cause an immunotoxic oral mucosa injury [19].

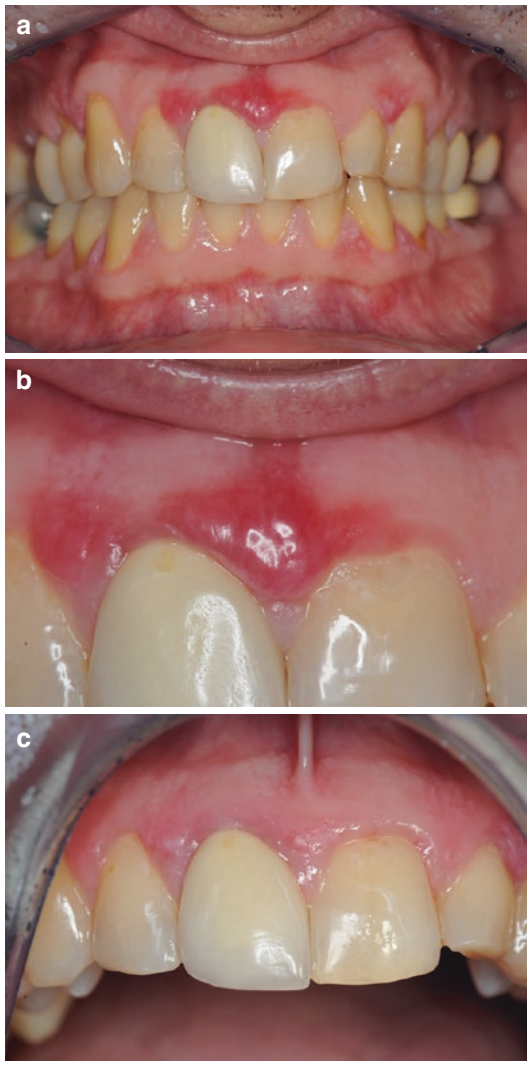

Fig. 31.1 Oral lichen planus, histologically confirmed, caused by mercury-containing dental amalgam fillings. (**a**, **b**) Oral lichen planus in a 44-year-old man with allergy to mercury amalgam (score grade, +; 20% in petrolatum). Before amalgam-removal treatment, the concentration of mercury in saliva sample was elevated (29.7 micrograms Hg per liter, threshold limit value of total mercury in saliva is <2.7 micrograms Hg per liter). (**c**) Healing of oral lichen planus 12 months after removal of the patient's three mercury dental amalgam tooth fillings. In this case, no topographical association was found between lesions and mercury amalgam fillings

31.4.3 Burning Mouth Syndrome (BMS) and Mercury Allergy

Burning mouth syndrome (BMS), also termed burning mouth disorders (BMD), is a quite common neurologic disorder involving both sensory components of the trigeminal nerve in adults over the age of 50 [21]. The disorder is 3–5 times more common in women than in men. The combination of symptoms is manifested clinically as an uncomfortable, continuous sensation of burning of the oral cavity and distressing dysesthetic pain, especially involving the tip of the tongue [21, 22]. Its exact cause is poorly understood and (multiple) drug treatment is often unsatisfactory. Recent studies suggest that the mechanism underlying these pains involves peripheral neuropathy [10, 22]. Mercury (Hg) and other nonessential toxic metallic elements are considered neurotoxic [2]. Strong evidence demonstrates that the myelin sheath and axon are the targets of damage by metals [21]. In addition, it is interesting to observe that nearly half of BMS patients may have a positive patch test to metals, suggesting an association with allergy as well [23–25].

31.4.4 Acrodynia

Acrodynia (also termed "pink disease") is characterized by a reaction to mercury compounds after prolonged exposure, in particular as a response to mercurous mercury (calomel, a bivalent inorganic mercury salt), which has been added to teething powder or deworming drugs in infants and children [2, 4] (Table 31.2). The aggregate signs and symptoms associated with acrodynia were also described in babies, infants, or in children who were in contact with diapers treated with phenyl mercury, an antiseptic used in the past, during diaper washes [2]. Frequent

Table 31.2 Sources of exposure to mercury compounds

	Type of exposure	Chemical forms of mercury	References
1	Alternative medicine	Mercury (metallic), mercury (inorganic compounds)	[2]
2	Fish consumption (Hg contaminated)	Organic mercury (methyl mercury), inorganic mercury	[2–4]
3	Folk medicine	Mercury (liquid metallic), mercury (inorganic compounds)	[2]
4	Homeopathy	Mercury (inorganic compounds)	[81, 82]
5	Mercury-containing ayurvedic medicines	Mercury (liquid metallic), mercury (inorganic compounds)	[83]
6	Occupational exposure	Mercury (liquid metallic), mercury (inorganic compounds)	[2]
7	Religious/ethnic practices	Mercury (liquid metallic), mercury (inorganic compounds)	[2]
8	Skin lightening creams	Inorganic mercury	[30, 84]

clinical signs and symptoms are: erythematous rash; fever; hypersialorrhea; gingivitis; oral ulcers; tooth loss; swollen red feet and hands; desquamating hyperkeratosis or "peeling hands"; lichenified plaques with excoriation and sometimes even trichotillomania secondary to pruritus; painful pink hands associated with transient "pink" skin rashes (on the trunk, legs, and arms); paresthesias of the feet and hands, which are cold, sweaty, and very tender to the touch; excessive perspiration; vasodilation; and cardiovascular imbalance with hypertension followed by tachycardia. Splenomegaly, lymphadenopathy, and neurologic deterioration (i.e., listlessness, anorexia, lethargy, irritability, insomnia, severe weakness, hypotonia, photophobia, and weight loss) may also be seen [2, 4, 5, 26, 27].

It is interesting to note that acrodynia has been hypothesized to be caused by an allergic, immunotoxic, or autoimmune reaction to mercury compounds in susceptible individuals [4, 5, 26]. All forms of mercury are potentially implicated as possible causes of acrodynia (i.e., organomercurials, inorganic mercury salts such as calomel, ammoniate mercury salts, mercury oxide) [5]. Nowadays, acrodynia is considered to be a rare condition [4, 5, 28].

In the past, acrodynia affected 1 in 500 babies when exposed to inorganic mercury salts [2, 4]. Two children with acrodynia-induced persistent pains were reported to benefit from the drug carbamazepine, a sodium channel blocker [4]. Of note, they continued to have marked and refractory pain despite the intravenous chelating agent D-penicillamine and repeated courses of analgesics prior to the administration of carbamazepine [4].

31.4.5 Kawasaki Disease

Inorganic mercury exposure may induce another immunotoxic response: Kawasaki disease (also termed mucocutaneous lymph node syndrome), a medium vessel vasculitis appearing in early childhood most commonly in children of Asian and Pacific Islander descent that is often accompanied by eosinophilia. After the initial description of Kawasaki disease in 1974 [29], various published reports indicated a putative link between mercury immunotoxicity and the syndrome [26, 30].

Interestingly, the clinical toxicological features of inorganic mercury toxicity and acrodynia resemble those of Kawasaki disease, which include: high-grade and persistent fever; photophobia; dry conjunctivitis; conjunctival injection; sore throat; oral lesions (ulcers); strawberry tongue; cracked and fissured lips; skin rashes (maculopapular); exfoliative keratolysis (focal

palmar peeling of the hands and soles); peripheral vascular disease; edema of the feet and hands; atrial tachycardia; coronary aneurisms; and the involvement of lymphoid tissues (i.e., lymphadenitis and cervical lymphadenopathy) [4, 26, 31]. Thus, acrodynia should be taken into account in the differential diagnosis [4].

The sources of elemental and inorganic mercury reported to be associated with Kawasaki's include a mercurial skin lightening cream, a broken thermometer, folk and alternative complementary medicine, and chemical compounds [32]. Hence, mercury seems to be an important environmental trigger that may induce this syndrome in genetically susceptible individuals [2, 5].

In some cases, there have been idiosyncratic reactions to mercury even at very low doses, stimulating a systemic hyperimmune response to mercury [26, 30]. Mercury has been associated with increased serum IgE levels in patients with Kawasaki syndrome [33]. Also, patients with Kawasaki syndrome have shown higher levels of mercury in urine compared to controls [34]. Toxicologically, with regard to acrodynia, the main feature that distinguishes these two mercury-related illnesses appears to be the total mercury concentrations in urine. Altogether, acute and/or chronic exposure to mercury should be considered a risk factor for Kawasaki syndrome in infants and children, although the exact relationship is currently unclear.

31.4.6 Mercury Allergy and Heart Disease

Chronic (long-term) mercury exposure through inhalation should be considered a risk factor for cardiovascular disease, cardiac dysrhythmia, labile pulse, tachycardia, cardiac conduction disorders, and hypertension. Further, the effects of exposure to mercury are well known in the science of trace elements, and the consequences of such exposure may include restrictive cardiomyopathy (endomyocardial), coronary heart disease [35], and carotid atherosclerosis [2]. Also, the positive correlation between exposure to mercury and the accumulation of this metal in a ventricular endomyocardial biopsy has been demonstrated [36].

In 2016, the apical ballooning syndrome Takotsubo syndrome, also termed stress-associated Takotsubo cardiomyopathy, was associated with a delayed-type hypersensitivity reaction to mercury [37]. Takotsubo syndrome is characterized by transient left ventricular systolic and diastolic dysfunction and usually manifests with severe chest pain. It has been diagnosed in about 1% of patients with acute chest syndrome and ST segment elevation on electrocardiogram. A recent small study involving 24 Takotsubo patients [37] showed that the results of the lymphocyte transformation test (LTT-MELISA® test) were positive for the mercury allergen in 45.8% of cases [37].

31.4.7 Tattoo Allergy

Allergic reactions to inorganic mercury (mercury II sulfide (HgS) known as "native vermilion") in red tattoo pigment have been reported, manifesting with intractable pruritus (Table 31.3) [38, 39]. Bilateral axillary reactive lymphadenopathy in association with tattoos has also been reported [40]. With continued exposure, metal particles (i.e., mercury, chromium, nickel) may be transported from the skin/tissue via the lymphatic system and then phagocytosed by macrophages, resulting in lymphadenopathy [40, 41]. Lymphadenopathy associated with metals is thought to be mediated by a delayed-type (type IV) hypersensitivity reaction to metal salts retained in the skin and sequestrated into lymph nodes [41–43].

Skin patch testing provides evidence of a delayed-type hypersensitivity reaction to the mercury present in red tattoo pigment in the form of mercury (II) sulfide (cinnabar) [44, 45]. In order to verify the diagnosis of allergic sensitization to mercury (HgS) and identify the culprit, patch testing and/or the LTT test should be performed as part of the initial work-up [44].

Table 31.3 Cutaneous lesions due to mercury in skin tattoos

	Skin tattoo-related diseases	Chemical compounds of mercury	References
1	Allergic reactions (red tattoo)	Inorganic mercury (HgS)	[85]
2	Cutaneous lymphoid hyperplasia (pseudolymphoma)	Inorganic mercury (HgS)	[86–88]
3	Dermatitis	Inorganic mercury (HgS)	[39]
4	Discoid lupus erythematosus (DLE)	Inorganic mercury (HgS)	[95]
5	Granulomatous reactions (sarcoid)	Inorganic mercury (HgS)	[89–94]
6	Lichenoid lesions	Inorganic mercury (HgS)	[44]
7	Nodular/verrucous lesions	Inorganic mercury (HgS)	[96]
8	Verrucous carcinoma	Inorganic mercury (HgS)	[97, 98]

Intradermal testing for mercury allergens should not be considered safe [46].

31.5 Assessment and Management of Hypersensitivity Responses to Mercury

Patients with signs and symptoms of hypersensitivity reactions to mercury should be referred to a specialist in allergology and/or dermatology. The differential diagnosis is quite broad, and a high index of suspicion is very important. An accurate, complete, and careful medical as well as dental history will help in diagnosing patients with clear risk factors for reaction to mercury (Tables 31.4 and 31.5).

31.5.1 Skin Patch Testing

In clinical practice, patch testing is considered to be the gold standard for the diagnosis of contact allergy to mercury. Recommended patch testing allergens are shown in Table 31.6. Skin patch testing demonstrates a delayed type hypersensitivity to mercury, i.e., elemental, metallic form mercury (Hg^0), inorganic mercury as mercuric chloride [(mercuric (II) chloride ($HgCl_2$) also "termed mercury two")] ($HgCl_2$), mercury dental amalgam, and alkyl mercurial compounds such as thimerosal (EtHg, $CH_3CH_2Hg^+$) and phenyl mercuric acetate ($C_8H_8HgO_2$). The waning of the positive patch test reaction may be slow, and a positive skin patch test—especially to mercury dental amalgam—likely suggests a strong, important, and pervasive allergy to mercury compounds. Clinicians should offer skin patch testing to mercury compounds as a diagnostic test for mercury allergy. Whenever possible, clinical relevance should be established. For example, some mercurial compounds such as thimerosal may not have as much current clinical relevance [47]. Nonetheless, certain forms of mercury, e.g., ethyl mercury, may accumulate in oral tissue and promote allergic sensitization, which may be relevant even at low systemic levels [24].

31.5.1.1 Interactions Between Mercury and Other Metals

There is evidence that gold may cross-react with mercury with a frequency of at least 10% [48–50]. In addition, chromium allergy has a conservative estimated prevalence of 15.4% in the female cohort [10]. From 2001 to 2013, the prevalence of allergy to chromium increased significantly in a select subgroup of patients with multiple chemical sensitivities exposed to mercury [10].

There is preliminary evidence of co-reactivity between mercury and titanium in humans, as previously described [10]. The prevalence of allergy to titanium (10.2%, 14 of 137) was detected among a cohort of 137 patients who have allergy to mercury [10].

31.5.1.2 Interactions Between Mercury and Drugs

Cross-reactivity exists between thimerosal and piroxicam [51–54]. Piroxicam should be avoided in patients who have allergy to thimerosal.

Table 31.4 Skin disorders associated with exposure to mercury in humans

	Skin manifestations	Chemical compounds of mercury	References
1	Acne	Mercury (metallic, vapors)	[39]
2	Acrodynia (pink disease, acrodynic erythema)	Metallic (inorganic) mercury and organic mercury	[10, 27, 28, 30, 99–102]
3	Alopecia areata	Mercury (elemental, vapors)	[26, 39, 103]
4	Amalgam dermatitis	Mercury (elemental, vapors)	[79, 104–113]
5	Angioedema	Mercury (elemental, vapors)	[10, 39, 56, 63, 114–116]
6	Baboon syndrome (SDRIFE)	Mercury (inorganic compounds, mercury vapors)	[22, 26, 81, 115, 117–119]
7	Blistering (bullous) disorders	Organomercurials, mercury (inorganic compounds)	[82, 120–122]
8	Dermatitis (anal)	Mercury (metallic, elemental, vapors), mercury (inorganic compounds)	[123]
9	Dermatitis (atopic)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[113, 124–126]
10	Dermatitis (contact)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 111, 127–129]
11	Dermatitis (other)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 26, 39, 79, 106, 112, 130]
12	Dermatitis (venenata)	Organomercurials	[131]
13	Dermographism (mercurialis)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[5, 10, 132]
14	Eczema (see also ‘Dermatitis’ above)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[23, 104, 107, 133–135]
15	Edema (facial swelling, periorbital)	Mercury (metallic), mercury (inorganic compounds)	[39, 63, 109, 132, 135]
16	Erysipelas-like mercury exanthem	Mercury (metallic), mercury (inorganic compounds)	[124, 136]
17	Erythema (mercury erythema)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[132, 137–140]
18	Erythema multiforme (EM)	Mercury (metallic), mercury (inorganic compounds)	[32, 128, 141–144]
19	Erythema nodosum	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[142, 145]
20	Exanthem (salmon and/or pink)	Mercury (metallic), mercury (inorganic compounds)	[10, 32, 117, 128, 143, 146–148]
21	Fungal infection (cutaneous)	Mercury (metallic), mercury (inorganic compounds)	[10, 39]
22	Geographic tongue (migratory glossitis)	Mercury (metallic), mercury (inorganic compounds)	[73, 149]
23	Granulomatosis with polyangiitis (Wegener’s granulomatosis)	Mercury (metallic), mercury (inorganic compounds)	[25]
24	Granulomatous reaction (mercury cutaneous)	Mercury (metallic), mercury (inorganic compounds)	[92, 150]
25	Grover’s disease (transient acantholytic dermatosis)	Mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 151]
26	Herpes simplex infection (cold sores)	Mercury (elemental, vapors), mercury (inorganic compounds)	[111, 132, 152]

(continued)

Table 31.4 (continued)

	Skin manifestations	Chemical compounds of mercury	References
27	Hyperpigmentation (mucocutaneous)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 26, 39, 59, 153]
28	Kawasaki disease (mucocutaneous lymph node syndrome)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[26, 27, 30, 32, 33]
29	Lichen planus (cutaneous/genital)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[10, 15, 39, 75, 154, 155]
30	Lymphadenitis (cervical or mesenteric)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[10, 39, 156, 157]
31	Mercury exanthem	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[22, 26, 79, 113, 117, 128, 132, 137, 143, 144, 146, 147, 158]
32	Nummular eczema (discoid eczema)	Mercury (elemental, vapors), mercury (inorganic compounds)	[10, 159–161]
33	Nummular lichenoid dermatitis	Mercury (elemental, vapors), mercury (inorganic compounds)	[160, 161]
34	Palmar erythema	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[162–164]
35	Palmoplantar pustulosis	Mercury (elemental, vapors), mercury (inorganic compounds)	[138, 148, 153, 163, 164]
36	Pemphigoid (bullous)	Mercury (inorganic compounds)	[82, 139]
37	Pemphigus foliaceus, endemic (fogo selvagem)	Organomercurials	[139, 165]
38	Pigmentary changes	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[5, 26, 39]
39	Pompholyx, dyshidrotic dermatitis	Mercury (elemental, vapors), mercury (inorganic compounds)	[155, 163]
40	Psoriasis/psoriatic manifestations	Mercury (elemental, vapors), mercury (inorganic compounds)	[108, 166, 167]
41	Scleroderma (systemic sclerosis)	Mercury (elemental, vapors), mercury (inorganic compounds)	[168]
42	Sebaceous hyperplasia (hyperplastic sweat glands)	Mercury (inorganic compounds), organomercurials	[26]
43	Skin rashes	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 26, 85, 107, 128]
44	Systemic allergic contact dermatitis	Mercury (elemental, vapors), mercury (inorganic compounds)	[10, 22, 64, 71, 85, 108, 117, 127, 128, 132, 158, 169–172]
45	Urticaria	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 39, 73, 106, 108, 143, 173]
46	Urticaria, papular urticaria	Mercury (elemental, vapors), mercury (inorganic compounds)	[120, 121, 174]
47	Vaccine-related vesicular eruption	Organomercurials (thimerosal)	[175–178]

Table 31.5 Oral diseases and conditions associated with exposure to mercury in humans

	Oral diseases	Chemical forms of mercury	References
1	Amalgam tattoo (Hg amalgam tattoo)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), methyl mercury	[10, 91, 179]
2	Angioedema (acute/recurrent)	Mercury (elemental, vapors), mercury (inorganic compounds)	[10, 56, 114–116]
3	Aspergillosis (sinus)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[180]
4	Atypical facial pain (persistent idiopathic facial pain)	Mercury (elemental, vapors), organomercurials	[10, 152, 181]
5	Black hairy tongue (lingua nigra villosa)	Mercury (elemental, vapors)	[182]
6	Burning lips syndrome	Mercury (elemental, vapors), mercury (metallic)	[210]
7	Burning mouth syndrome (BMS)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 22, 23, 59, 114, 115, 135, 144, 152, 183–186]
8	Cheilitis (allergic contact, angular and recurrent)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[23, 108, 135, 187–190]
9	Cheilitis (exfoliative)	Mercury (elemental, vapors), mercury (inorganic compounds)	[187]
10	Cheilitis granulomatosa	Mercury (elemental, vapors)	[191]
11	Dermographism (oral)	Mercury (elemental, vapors), mercury (inorganic compounds)	[39]
12	Dysgeusia (metallic taste)	Mercury (elemental, vapors), mercury (inorganic compounds)	[10, 22, 192, 193]
13	Edema (facial, periorbital)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[63, 132]
14	Erythematous oral lesions	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[10, 194]
15	Facial dermatitis (exudative)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[132]
16	Gingivitis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[10, 73, 155, 185, 195–198]
17	Gingivitis (plasma cell gingivitis)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[199]
18	Glossitis	Mercury (elemental, vapors), mercury (metallic)	[149, 192, 197, 200]
19	Glossitis (migratory/palate erythema migrans)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[149]

(continued)

Table 31.5 (continued)

	Oral diseases	Chemical forms of mercury	References
20	Glossodynia	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[22, 114]
21	Intraoral contact hypersensitivity	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[23, 114, 188–190]
22	Itching (pruritus) of the oral cavity	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 122, 201]
23	Leukoedema	Mercury (elemental, vapors)	[115]
24	Lichenoid contact stomatitis (or oral lichenoid lesions)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[67, 68, 74, 154, 202–209]
25	Lips (dry, chapped, cracked, sore lips)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[23, 142, 187, 189, 210]
26	Oral cancer	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[213–216]
27	Oral dysesthesia	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 217]
28	Oral leukoplakia (leukokeratosis)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[56, 114, 115, 202, 203, 218, 219]
29	Oral lichen planus (OLP)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[18, 23, 67–70, 73–75, 154, 155, 205–208, 220, 221]
30	Oral melanosis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[26, 78]
31	Oral thrush (oral candidiasis)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 26, 39]
32	Oral ulcers	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[115, 145, 188, 205, 222]
33	Orofacial granulomatosis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[23, 205, 223–226]
34	Periodontitis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[75, 189, 196, 227]
35	Perioral dermatitis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[23, 73, 185, 187]
36	Perioral paresthesia	Mercury (elemental, vapors), organomercurials	[10, 210, 217]
37	Pharyngitis	Mercury (elemental, vapors)	[59]
38	Polypous hyperplasia—oral mucosa	Mercury (elemental, vapors)	[228]
39	Pruritus (neuropathic)	Mercury (elemental, vapors)	[10, 105, 107, 201]

Table 31.5 (continued)

	Oral diseases	Chemical forms of mercury	References
40	Recurrent aphthous ulcers (RAU)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[10, 39, 75, 185, 205, 222, 229]
41	Sialorrhea (hypersalivation)	Mercury (elemental, vapors)	[5, 10, 39]
42	Sloughing/peeling of the oral mucosa	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[230]
43	Stomatitis (contact)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10, 23, 39, 112, 114, 169, 189, 198, 219, 231]
44	Systemic lupusery thematosus (SLE)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[78, 84, 211, 212]
45	Trigeminal neuralgia	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[10, 15, 21]
46	Tooth loss	Inorganic mercury salts	[5, 26]
47	White oral lesions	Mercury (elemental, vapors)	[145, 218, 220]
48	Xerostomia (dry mouth)	Mercury (elemental, vapors)	[10, 22, 152, 192, 193]

Table 31.6 Recommended dental patch test allergens in patients with suspected allergy to mercury and other metallic elements contained in mercury dental amalgam

	Allergen concentration	Chemical element	%	Vehicle	References
1	Mercury	Hg	0.5	Petrolatum	[19, 48, 232, 233]
2	Mercury chloride	Hg (II) chloride	0.1	Petrolatum	[19, 48, 232, 233]
3	Ammoniated mercury	ClH_2HgN	1.0	Petrolatum	[19, 48, 232, 233]
4	Thimerosal	$C_9H_9HgNaO_2S$	0.05	Petrolatum	[19, 48, 232, 233]
5	Phenylmercury	$C_8H_8HgO_2$	0.01	Petrolatum	[19, 48, 232, 233]
6	Amalgam		5.0	Petrolatum	[19, 48, 232, 233]
7	Amalgam		20.0	Petrolatum	[19, 48, 232, 233]
8	Cobalt chloride	Co	1.0	Petrolatum	[19, 234]
9	Gold sodium thiosulfate	Au	0.5	Petrolatum	[19]
10	Nickel sulfate	Ni	5.0	Petrolatum	[19, 229]
11	Copper sulfate	Co	2.0	Petrolatum	[233]
12	Palladium chloride	Pd	2.0	Petrolatum	[235]
13	Silver nitrate	Ag	1.0	Petrolatum	[233]
14	Tin chloride	Sn	50.0	Petrolatum	[233]
15	Zinc	Zn	2.5	Petrolatum	[19]

31.5.2 Immunological Assay: The Lymphocyte Transformation Test (LTT)

The LTT is an in vitro test of metal sensitivity in patients with allergic conditions. In peripheral blood lymphocyte cultures, metal antigens (i.e., inorganic and organic compounds) are able to induce mitosis, transforming the lymphocytes. LTT should be seen as complementary to patch testing [10]. The optimal sequence of allergological testing should be as follows: first, skin patch testing and, second, in vitro LTT.

31.5.3 Susceptibility for Allergy to Mercury

The various chemical forms of mercury (mercury vapor, inorganic mercury ions, and organic mercury) associated with mercury dental amalgam, for the most part, appear to affect the immune system first, and only subsequently the nervous system and other organs and tissue [55]. Researchers have identified some major histocompatibility complex (MHC) class II alleles or HLA haplotypes that could be involved in the pathogenesis of immunotoxic and other reactions to mercury. Some authors have reported an increased frequency of HLA class II alleles DRB1*07 [15, 56, 57] and DRB1*04 [58] among patients with contact hypersensitivity reactions to mercury and mercury adverse health effects [1, 59] (Table 31.7). Additionally, the data indicate that deletion of genetic material may confer risk of susceptibility to thimerosal sensitization [60]. In humans, subjects with a positive allergic reaction to thimerosal were homozygous for a deletion in genes for the glutathione S-transferases M1 (GSTM1) and T1 (GSTT1) [60]. GSTM1 (mu class) and GSTT1 (theta class) genes are involved in the detoxification process of mercury (Table 31.7).

31.5.4 Removal of Mercury Amalgam from Patients with Adverse Health Effects

Removal of mercury-containing dental amalgam fillings should be considered in cases of allergy to mercury [10, 56]. The procedure can be performed safely in high-risk populations; for example, individuals with oral lichen planus, angioedema and anaphylactic reactions, autoimmune diseases, multiple sclerosis, kidney disease, and pregnant and lactating women [10, 56, 61].

The lift-on technique, in which the entire mercury filling is removed en bloc, is the standard procedure for removing mercury amalgam tooth restorations and has been performed since 1997 for patients with strong allergy to mercury amalgam with local (oral) and/or systemic diseases related to mercury dental amalgam [56]. In fact, in appropriately selected patients who are operated on by experienced dentists, the lift-on technique should be considered the new gold standard

Table 31.7 Genetics of mercury allergy

	Genetic risk factors	Mercury chemical compounds	References
1	CPOX4	Compounds of mercury	[236]
2	GSTM1-GSTT1	Organic mercury (Thimerosal)	[60]
3	HLA-DRB1*04	Metallic mercury, inorganic mercury, organic mercury	[15, 57–59]
4	HLA-DRB1*07	Metallic mercury, inorganic mercury, organic mercury	[15, 57–59]
5	Methylenetetrahydrofolate reductase (MTHFR)	Inorganic mercury compounds	[102]
6	Paraoxonase 1 (PON1)	Compounds of mercury	[102]

The association of hypersensitivity to mercury with HLA-linked genes (particularly HLA-DRB1*) suggests that both genetic and immunologic factors have a role in the development of disease

[10, 56, 62]. This is an effective and well-tolerated technique that has the goal of blocking the release of metal vapor from amalgam surfaces and reversing allergic inflammation due to mercury [10, 19].

The effectiveness and safety of dental amalgam removal for oral lichen planus associated with allergic sensitization to mercury amalgam have been well studied in the last decades. Recovery time after amalgam removal for mercury allergy-related OLP is about 3–12 months, with a mean time to resolution of 6 months. One report also showed that the procedure was safe and effective in the case of a patient who had mercury amalgam-induced anaphylaxis [63].

31.5.5 Dietary Intervention for Patients with Allergy to Mercury

Modification of diet is a medical intervention and should be a routine component of any attempt to reduce (1) the body mercury burden, (2) oxidative stress, and (3) allergic sensitization to mercury compounds in humans [64]. Absorption of mercury is believed to be pH dependent, and an increase in intestinal pH has been shown to increase gastrointestinal inorganic mercury absorption in an animal model.

Long-lived predatory fish should generally be avoided, in order to lower the risk of mercury exposure (Table 31.2). Treatment with a low-mercury diet consisting of avoidance of all products containing fish and seafood should be conducted for months before retesting mercury levels.

31.6 Concluding Thoughts and Further Considerations

Allergy to mercury is now recognized as a common and often overlooked type IV hypersensitivity disorder, with an estimated prevalence of 5–16% in the general population of industrialized nations [8, 65]. However, a large Danish study showed that only 0.5% of adults aged 18–69 years had thimerosal allergy [8]. Recent studies with a select sample of mercury amalgam-associated adverse events estimated the prevalence of allergy to mercury compounds at 25.8–34.6% [1]. This prevalence is consistent with reports of allergic sensitization to mercury in patients with oral disease (i.e. OLP, BMS) [66–71]. Among the cases of OLP, the prevalence of mercury allergy to at least one dental mercury patch test allergen ranged from 16 to 62%, whereas the frequency of mercury sensitization in the general population is about 1–4% [72]. The clinical implications of an increased risk of oral and/or systemic disease associated with exposure and allergy to mercury have immediate relevance for clinical practice.

In the past, type III hypersensitivity reactions (or Arthus-type reactions) with antigen–antibody complexes have been reported rarely by patients who had been exposed to mercury (primarily mercury vapors) [5, 73, 74]. The constituent immune complexes consist of IgG and mercury compound antigens. Examples include an anti-basement membrane glomerulonephritis and may be followed by a superimposed immune complex glomerulonephritis [5, 75], hypersensitivity pneumonitis, and dermatographic urticaria [76]. Type III hypersensitivity reactions also accounted for 10% of reported laboratory-confirmed cases of adverse events to mercury-containing dental amalgam fillings attributable to allergic sensitization to mercury [12]. Dental amalgam can also cause extreme type I hypersensitivity reactions, which may lead to mercury amalgam-related anaphylaxis [63].

A genetic contribution to allergic sensitization to mercury has been well documented, suggesting that genetic polymorphisms in GSTM1 and GSTT1 genes as well as MHC class II molecules bestow susceptibility to mercury sensitization and increased mercury retention kinetics [59, 60]. The genetics underlying susceptibility to allergy to mercury compounds are shown in Table 31.7.

Hypersensitivity to mercury may play a role in triggering autoimmune systemic processes [77]. Recent evidence has suggested an association between allergic sensitization to mercury and autoimmunity [77, 78] (Tables 31.8 and 31.9). Long-term exposure to mercury may lead to overactivity of T lymphocytes. Further study is required on this topic.

Some signs and symptoms associated with allergic sensitization to mercury compounds are responsive to oral H1 antihistamine therapy [79, 80], which is well tolerated. In contrast, adverse events to corticosteroid therapy are frequent, especially if associated with coexposure to titanium (Ti) dental implants, even with short-term use.

Table 31.4 lists clinical conditions with skin manifestations that have been associated with exposure to mercury. Table 31.5 lists oral diseases and immunoallergic reactions that have been associated with exposure to mercury compounds. For completeness, classic clinical signs and symptoms related to overexposure to mercury are shown in Table 31.10.

Clinicians should recognize early stages of allergy or toxicity to mercury, and recent advances in laboratory methods may facilitate diagnosis of sequelae related to mercury exposure and improve the care of patients with allergy to mercury.

Table 31.8 Further testing to be considered in patients with mercury sensitization

	Recommended testing in patients with allergy to mercury	References
1	Angiotensin-converting enzyme (ACE)—serum	[12]
2	Anticardiolipin antibodies—serum	[12]
3	Anti-glomerular basement membrane (anti-GBM IgG)—serum	[1, 75]
4	Antineutrophil cytoplasmic antibodies (c-ANCA, p-ANCA)—serum	[1, 12]
5	Antinuclear (ANA) and antinucleolar (ANoA) antibodies—serum	[1, 12, 17]
6	Beta-2 microglobulin—serum (B2M)	[237]
7	C3 complement—serum	[1, 115]
8	CD69 (T cell subset in peripheral blood)	[15]
9	Eosinophil count in peripheral blood (eosinophilia)	[1, 15, 144, 199, 237, 238]
10	Gamma-globulins—serum	[1, 15]
11	Immune complexes (CIC)—serum (immune complex diseases)	[12, 17]
12	Immunoglobulin E (IgE)—serum	[237, 239]
13	Immunoglobulin G (IgG)—serum (hypergammaglobulinemia)	[1, 15, 17, 239]
14	Immunoglobulin G1 (IgG1)—serum	[239]
15	Interleukin 2 receptor (sIL2R)—serum soluble	[1, 10, 63, 240]
16	Neuron-specific enolase (NSE)—serum	[1, 241]
17	Polyclonal B cell activation (IgA-IgE-IgM)—serum	[1, 5]

Table 31.9 Chemical forms of mercury that have been associated with autoimmunity

	Clinical manifestations	Chemical forms of mercury	Antigenic determinant	References
1	Fever, skin rash, glomerulonephritis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	Glomerular basement membrane (IgA, IgG, IgM)	[5, 75]
2	Hashimoto's thyroiditis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	Antithyroid autoantibodies, thyroid peroxidase antibodies (TPO)	[167]
3	Lupus, vasculitis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	Cardiolipin	[12]
4	Myelin disorders	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	Myelin basic protein (MBP)	[17, 242]

Table 31.9 (continued)

	Clinical manifestations	Chemical forms of mercury	Antigenic determinant	References
5	Nephritic immune complex	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)		[243]
6	Mixed connective-tissue disease	Thimerosal, mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	URP3—fibrillarin	[168]
7	Scleroderma	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	URP3—fibrillarin	[168]
8	Vasculitis	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	c-ANCA, p-ANCA	[12]

Table 31.10 Mercury-related signs and symptoms in patients with acute and/or chronic exposure

	Clinical conditions related to mercury overexposure in humans	Mercury chemical compounds	References
Inorganic mercury			
1	Amalgam-induced anaphylaxis	Mercury (elemental, vapors)	[63]
2	Anaphylactic shock	Mercury (elemental, vapors), mercurochrome (dibromohydroxymercurifluorescein)	[63, 116, 174, 244]
3	Anorexia mercurialis	Mercury (elemental, vapors)	[2, 5, 10]
4	Anxiety	Mercury (elemental, vapors)	[5]
5	Asthma (bronchial)	Mercury (elemental, vapors)	[134]
6	Cardiomyopathy (restrictive)	Mercury (inorganic compounds)	[5]
7	Chronic fatigue syndrome (CFS)	Mercury (elemental, vapors)	[5, 10]
8	Dermographism mercurialis	Mercury (elemental, vapors)	[5]
9	DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Mercury compounds	[28]
10	Erethymus mercurialis (erethism)	Mercury (elemental, vapors)	[2, 5]
11	Fever of unknown origin (FUO)	Mercury (elemental, vapors)	[10]
12	Forgetfulness	Mercury (elemental, vapors), organomercurials	[2, 10]
13	Gastrointestinal disorders	Mercury (elemental, vapors)	[5, 10]
14	Gingivitis	Mercury (elemental, vapors)	[2, 5, 10]
15	Headache	Mercury (elemental, vapors)	[5, 10]
16	Hearing loss	Mercury (elemental, vapors)	[61]
17	Hunter–Russell syndrome	Methyl mercury, organomercurials	[2, 5]
18	Hyperhidrosis (excessive sweating)	Mercury (elemental, vapors)	[10, 143]
19	Loss of weight	Mercury (elemental, vapors)	[10]
20	Malaise	Mercury (elemental, vapors)	[5, 10]
21	Multiple chemical sensitivity (MCS)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[10]
22	Nephritic syndrome (proteinuria)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[243]
23	Neurasthenia	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[5, 10]

(continued)

Table 31.10 (continued)

	Clinical conditions related to mercury overexposure in humans	Mercury chemical compounds	References
24	Systemic autoimmunity	Inorganic mercury	[10, 84, 142]
25	Thyroid imbalance (i.e., hypothyroidism)	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds)	[5, 10]
26	Tremors (intentional/postural)	Mercury (elemental, vapors)	[5, 10]
27	Weakness	Mercury (elemental, vapors), mercury (metallic), mercury (inorganic compounds), organomercurials	[5, 10]
28	Young' syndrome (azoospermia, bronchiectasis)	Inorganic mercury	[245]
Organic mercury			
1	Ataxia (cerebellar)	Organomercurials	[5]
2	Dysarthria	Organomercurials	[5]
3	Dysphagia (myopathy)	Organomercurials	[2, 5]
4	Fetal methyl mercury syndrome	Organomercurials	[2, 5]
5	Paresthesia (mouth, lips, extremities)	Organomercurials	[2, 5, 10]
6	Spasticity	Organomercurials	[2, 5, 10]
7	Tremors	Organomercurials	[5, 10]
8	Vision loss (loss of peripheral vision)	Organomercurials	[2, 5, 10]

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Metal Allergy: Nickel

32

Carola Lidén

32.1 Introduction

Nickel is the most common skin sensitizer, affecting large proportions of women, men and children. Nickel allergy is considerably more prevalent among girls and women than boys and men, owing to differences in exposure patterns. Skin exposure to nickel in various consumer articles results in nickel allergy and allergic contact dermatitis on exposed body parts, including the hands. Occupational exposure to nickel is an important cause of occupational skin disease, particularly hand eczema.

Nickel is used in numerous products and materials, many of which come in contact with the skin of consumers and workers. The use of nickel in steels and plating started around 1870, and nickel production has increased considerably since 1940 [1–3]. Today, approximately 65% of the nickel produced is used in stainless steels, 20% in other steels and alloys, and 15% in plating and also in chemical compounds (Nickel Institute https://www.nickelinstitute.org/).

Many of the products and materials intended for consumer and occupational use release nickel ions upon skin contact and contaminate the skin. It is thus difficult to avoid skin exposure to nickel in daily life and in the workplace.

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32.2 Prevalence of Nickel Allergy

Results from some of the pioneering, largest and most recent studies on the prevalence of nickel allergy among dermatitis patients and the general population in Europe and North America are shown in Tables 32.1 and 32.2. Occupational groups affected by nickel allergy are shown in Table 32.3. There are large differences in the prevalence of nickel allergy between women and men and between age groups, countries and occupations, over time (Fig. 32.1). Most alarming is the persistent and high prevalence of nickel allergy and particularly the much higher prevalence among women compared with men.

32.2.1 Dermatitis Patients

Table 32.1 shows that nickel allergy is extremely common among patch-tested adult dermatitis patients (range 12–25%) and three to six times more frequent among women than men. The prevalence of nickel allergy in children is also very high; to what extent stricter selectivity in patch testing children as compared to adults affects the results is not known.

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Table 32.1 Prevalence of nickel allergy among dermatitis patients in European countries and North America. Examples to illustrate differences over time, between countries and genders

Study population, period (no. patch tested)	Nickel allergy			Reference
	Total (%)	Women (%)	Men (%)	
Adults, dermatitis patients				
Four European countries, 1985–2010 (n = 180,390)	–	–	–	[4]
Denmark, 1985–2010 (n = 19,828)	12.3	17.4	3.1	
Germany 1995–2010 (n = 104,933)	13.6	18.9	5.1	
Italy 1997–2010 (n = 20,231)	25.0	31.9	10.8	
UK 2002–2010 (n = 35,398)	17.7	23.4	6.2	
Sweden, 2009 (n = 3112)	17.6	<40 years, 23.3 ≥40 years, 24.7	<40 years, 6.1 ≥40 years, 6.0	[5]
Twelve European countries (ESSCA), 2009–2012 (n = 56,761)[a]	19.7	<40 years, 26.8% ≥40 years, 23.5%	<40 years, 8.4 ≥40 years, 6.5	[6, 7]
North America (NACDG), 2013–2014 (n = 4850)	20.1	–	–	[8]
Children, dermatitis patient				
Denmark, 1–17 years, 2003–2011 (n = 2587)	9.7	12.4	4.7	[9]
Eleven European countries (ESSCA), 1–16 years, 2002–2010 (n = 6583)[b]	16.7	–	–	[10]
North America (NACDG), 0–18 years, 2005–2012 (n = 874)	28.1	–	–	[11]

ESSCA European Surveillance System on Contact Allergies, *NACDG* North American Contact Dermatitis Group (Canada and the USA)

[a]Centres in Austria, Denmark, Finland, Germany, Italy, Lithuania, Poland, Slovenia, Spain, Switzerland, The Netherlands and the UK

[b]Centres in Austria, Denmark, Finland, Germany, Italy, Netherlands, Poland, Slovenia, Spain, Switzerland and the UK

Table 32.2 Prevalence of nickel allergy in the general population in European countries. Examples to illustrate differences over time, between countries and genders

Study population, period (no. patch tested)	Nickel allergy			Reference
	Total (%)	Women (%)	Men (%)	
Adults, general population				
Finland, 1976–1977 (n = 980)[a]	4.5	8.0	0.8	[12]
Denmark, 1990–1991 (n = 567)	6.7	11.1	2.2	[13]
Denmark, 2006 (n = 3460)	5.9	9.9	1.0	[14]
Five European countries, 2008–2011 (n = 3119)	14.5	22.2	5.2	[15]
Germany (n = 1024)	13.9	–	–	
Italy (n = 546)	16.4	–	–	
Portugal (n = 531)	18.5	–	–	
Sweden (n = 518)	8.3	–	–	
The Netherlands (n = 500)	15.8	–	–	
Children, general population				
Denmark, 12–16 years, 1995–1996 (n = 1146)	8.6	13.7	2.5	[16]
Sweden, 15–23 years, 2000–2004 (n = 4376)	9.9	13.3	2.5	[17]
Poland, 15 years, 2009–2010 (n = 528)	7.8	12.3	1.4	[18]
Sweden, 16 years, 2011–2013 (n = 2236)	7.5	9.8	4.9	[19]

[a]Including schoolchildren (n = 158)

Table 32.3 Examples of occupations with work-related nickel allergy and nickel dermatitis and sources of occupational exposure to nickel [2, 20–22]

Occupations, examples		Occupational nickel exposure, examples
Broad description	Job title	
Industrial setting	Electroplater, electronics industry worker, metalworker	Coins, coolants and cutting fluids, controls, construction materials, cutlery, electroplating fluids, equipment, handles, keys, kitchen utensils, locks, metal sheets, measuring cups, nails and screws, needles, nickel-plated earthing straps, pipes, tools, water taps, etc. See Table 32.4 for common and not occupation-specific exposures
Construction work, etc.	Car mechanic, carpenter, construction worker, electrician, locksmith, painter, plumber	
Service and healthcare	Bar staff, cashier, caterer, chef and cook, cleaner, guard, hairdresser, nurse, shop assistant, tailor	

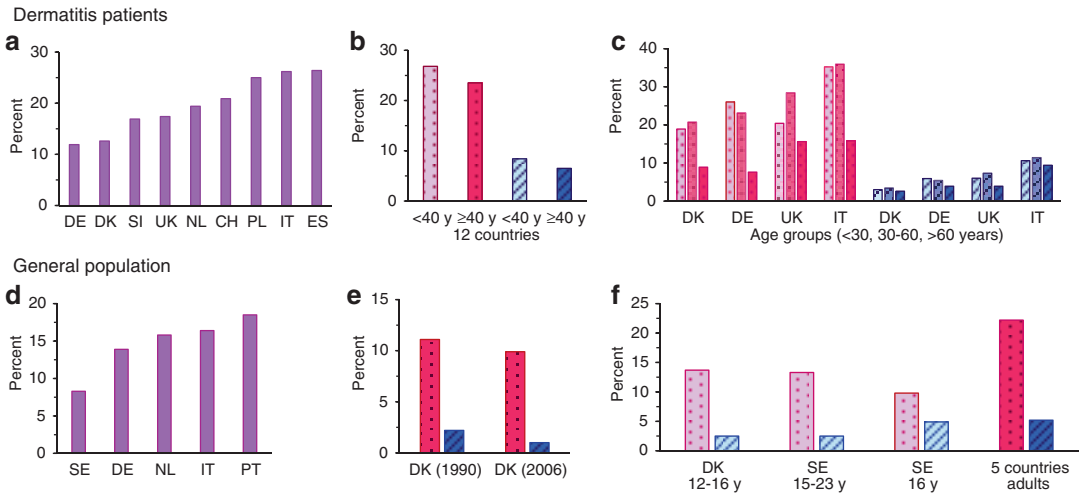

Fig. 32.1 Prevalence of nickel allergy among patch-tested dermatitis patients (**a**–**c**) and the general population (**d**–**f**) in Europe. Examples to display differences between countries, genders and age groups, over time. See also Tables 32.1 and 32.2. References: (**a**) [6]; (**b**) [7]; (**c**) [4]; (**d**) [15]; (**e**) [13, 14]; (**f**) [15–17, 19]. Country codes: *CH* Switzerland, *DE* Germany, *DK* Denmark, *ES* Spain, *IT* Italy, *NL* The Netherlands, *PL* Poland, *PT* Portugal, *SE* Sweden, *SI* Slovenia, *UK* United Kingdom. Colour codes: *red/dots*—women or girls, *blue/stripes*—men or boys, *violet*—all, *pale red or blue*—youngest, *medium red or blue*—middle, *dark red or blue*—oldest age group

32.2.2 General Population

There are few large patch test studies among the general population, compared with dermatitis patients. Table 32.2 shows that nickel allergy is extremely common among the general population, adults (range 5–19%) as well as children including adolescents (range 8–10%). Nickel allergy is four to ten times more frequent among women than men among the general population, and the prevalence differs largely also between girls and boys.

32.2.3 Geographical Differences

Healthcare and social security systems, access to dermatology and selection for patch testing, patch test routines, etc., vary between countries, which contribute to difficulties in comparing the prevalence of nickel allergy between countries. The highest prevalence rates among dermatitis patients in 12 European countries (Table 32.1, Fig. 32.1) were reported for Italy, Poland and Spain (25–26%) and the lowest for Denmark and

Germany (12–13%). In North America, the generally used patch test concentration of nickel is 2.5%, half the concentration of that used in the European baseline series. It is likely that this has resulted in some underestimation of nickel allergy among patch-tested patients in North America (Table 32.1).

Likewise, there are large differences between countries in the prevalence of nickel allergy among the general population (Table 32.2 and Fig. 32.1).

32.2.4 Time Trends

Studies where nickel allergy has been monitored over several years, or reevaluated under similar conditions, show convincingly that nickel allergy has started to decline in some countries. For dermatitis patients in Europe (Table 32.1), a significant decrease in nickel allergy has been noted among younger women (below age 30 or 40) in Denmark, Germany, Italy, Sweden and the UK, and an increase has been noted among women and men above this age in some of the countries (Fig. 32.1) [4, 5]. The reduced prevalence of nickel allergy in the younger age groups has been interpreted to be a result of the EU restriction of nickel and the increase in a cohort effect (see Chap. 5).

Only few studies allowing for trend analysis have been performed among the general population (Table 32.2, Fig. 32.1). A decrease in nickel allergy among the younger women was noted in Denmark between 1990/1991 and 2006; Denmark introduced a nickel restriction in 1991, 10 years before the EU [14].

For dermatitis patients in North America (Table 32.1), a significantly higher prevalence of nickel allergy has been recorded for the period 2013–2014 compared with 2001–2012 [8]. In a systematic review of peer-reviewed publications from the USA in 1961–2015, more than 18,000 adult nickel dermatitis cases were identified [29]. The number of published cases and articles had increased exponentially; suggested explanations for this were previous underdiagnosis and underreporting and increasing nickel exposure and sensitization. There is no nickel regulation in North America, and the North American Contact Dermatitis Group (NACDG) has suggested that regulations restricting release of nickel should be introduced also in North America.

Time trends in nickel exposure are discussed below.

32.3 Occupational Groups

Occupational nickel exposure is still an important risk factor for nickel allergy and related hand eczema, and certain occupational groups are affected more often than the general population [2, 3, 20]. Examples of occupational groups with a high frequency of nickel allergy are listed in Table 32.3.

More than a hundred years ago, nickel dermatitis was identified as an occupational skin disease among nickel platers. Until the 1930s nickel allergy was predominantly a male occupational disease. Improved industrial hygiene and technical development have decreased the risk, but safety standards vary significantly between workplaces, industries and countries. Outbreaks of nickel allergy are still reported in industrial settings involving platers, metalworkers and electronics industry workers. In such industries, the use of nickel or nickel chemicals is generally obvious and unavoidable (Table 32.3).

Many occupations in the construction industry or involving repair and maintenance work are associated with high exposure to nickel, resulting in occupational nickel allergy and nickel dermatitis (Table 32.3). Car mechanics, electricians, locksmiths, plumbers and other groups are exposed to nickel from intense contact with work materials, tools and other equipment, sometimes in conjunction with exposure to skin irritants.

The prevalence of nickel allergy and hand eczema is high in many occupations in the service and healthcare sectors (Table 32.3). Exposure to nickel in these occupations is often not as obvious as in the other groups. Exposure may be caused by repeated contact of short duration with

various commonly occurring items, including coins, handles, keys and utensils (Table 32.4). Exposure to wet work and other irritant factors in many of these occupations impairs the skin barrier function, which facilitates penetration of nickel, sensitization and dermatitis. It has, however, sometimes been questioned whether or not the high rate of nickel allergy in female-dominated occupations such as hairdressing, cleaning and nursing is work related.

Table 32.4 Types of metallic items, including those listed in the nickel restriction by REACH, known to release nickel and to cause nickel allergy and dermatitis. Examples, beyond those listed in the restriction, mainly from reviews [2, 23, 24], market surveys [25–28] and patient-based studies [29, 30] are provided

Category	Type
Examples listed in the EU nickel restriction[a]	Any post assemblies inserted into pierced parts of the body; articles intended for direct and prolonged contact with the skin such as earrings, necklaces, bracelets and chains, anklets, finger rings, wristwatch cases, watch straps and tighteners, rivet buttons, tighteners, rivets, zippers and metal marks in garments, spectacle frames[a]
Definition of "prolonged contact" in relation to the EU nickel restriction[b]	"Prolonged contact with the skin is defined as contact with the skin to articles containing nickel of potentially more than 10 min on three or more occasions within 2 weeks or 30 min on one or more occasions within 2 weeks"
Accessories	Bags, belt buckles, umbrellas, wallets
Coins	1 and 2 EUR, many national coins
Electronic devices	Activity bracelets, desktop computers, mobile phones,[a] laptops, play stations
Handheld tools	Cutting tools, files, measuring tools, pliers, saws, scissors, spanners
Musical instruments	Brass instruments, string instruments, wind instruments
Toys	Key chains, magnets, skate boards, tools
Utensils	Electronic cigarettes, handles, key chains, keys, kitchen utensils, knitting needles, needles, paint brushes, pens

[a]Entry 27 of Annex XVII to REACH: Nickel and its compounds. Spectacles were initially listed but subsequently transferred to the Medical Devices Directive. The European Chemicals Agency (ECHA) has explained (Q&A) that mobile phones are covered by the restriction.
[b]Definition by ECHA (Q&A) of "prolonged contact" in relation to the nickel restriction. A list of examples is to be published.

Two large studies in the UK in the 1990s assessed occupational contact dermatitis and nickel exposure. In 23% of 368 nickel-allergic patients, nickel was considered to be an occupational or possibly occupational allergen. The main workers were hairdressers, retail clerks, caterers, cleaners and metalworkers. Hand eczema was more prevalent in the occupational than nonoccupational group [21]. National occupational surveillance data was examined, and it was estimated that up to 12% of occupational contact dermatitis cases were associated with nickel exposure. Hairdressers, bar staff and chefs or cooks had the highest incidence rates [22].

Exposure assessments of the work environment are generally required to identify and validate the relevance of occupational nickel exposure (see Chap. 6).

32.4 Exposure

32.4.1 Sources of Skin Exposure

It is necessary to identify sources of nickel exposure in the workplace, home and leisure environment for exposure reduction and prevention of dermatitis. The dimethylglyoxime (DMG) test indicates the presence of nickel ions by a pink colour. For decades, it has been the most valuable tool that has been used in dermatology in testing for nickel release. It is used in the clinic, market surveys and workplace studies, and it has been standardized and validated in relation to the limit value (0.5 μg/cm^2/week) of the EU nickel restriction [31, 32] (see Chap. 6).

Examples of typical items known to release nickel and cause nickel allergy and dermatitis are given in Table 32.4. Numerous market surveys have been performed with the DMG test and only a few by nickel release in artificial

sweat. Most studies have examined jewellery or earrings; others have assessed coins, clothes, electronic devices, tools, toys and other articles. See Chaps. 13, 14, 15, and 16.

32.4.2 Nickel Release in Artificial Sweat

Nickel release from materials and items is of large interest for risk assessment, and it can be quantified by immersion in artificial sweat according to EN 1811, the reference test method for nickel restriction [33]. The rate (speed) of release of nickel from materials is initially very high and declines rapidly, and samples should preferably be taken at several time points: after minutes, hours, days and a week. The release rate is important for understanding why contact with coins, handles, tools and other items can result in deposition of significant amounts of nickel on the skin [34–36].

32.4.3 Trends in Exposure

Fashion varies over time, and fashion items, including suspenders, ear clips, jeans buttons and piercing jewellery, have been important for widespread nickel sensitization. Technical development in material design and introduction of new types of consumer articles, including electronic devices such as mobile phones, laptops, play stations, activity bracelets and electronic cigarettes, have been highlighted as new sources of nickel exposure and dermatitis among children, consumers and workers (Table 32.4 and Chap. 13).

Three consecutive surveys in Sweden show significant adaptation to the requirements of the Nickel Directive that entered into full force in 2001 (Table 32.4) [37–39]. In 1999, 25% of 725 articles were DMG test-positive, in 2002 8%, and in 2010 9% were DMG test-positive. Only 4% of the earrings were DMG test-positive in 1999 and 2010, and 0% in 2002, considerably lower than recorded in other countries (15–31%) [40]. Sweden introduced a restriction on the nickel concentration (0.05%) in piercing posts used during epithelization in 1990, corresponding to former part 1 of the Nickel Directive, and a nationwide information campaign about the Nickel Directive was launched in Sweden in 1999.

Notwithstanding the relatively good compliance to the restriction in Sweden, the prevalence of nickel allergy was high among 16-year-old girls (9.8%) and boys (4.9%) born in 1994–1996 [19]. Sources of exposure other than piercing, jewellery, etc., likely contributed significantly to their sensitization.

32.4.4 Sharpening of the EU Nickel Restriction

Owing to the slow decrease of nickel allergy in the EU despite the restriction, the European Chemicals Agency (ECHA) was requested to define what should be interpreted as “prolonged contact” in the regulation. In 2014, ECHA published this definition (Table 32.4). ECHA has also been requested to prepare a list of examples of articles covered by the definition, as a guideline. Many of the items in Tables 32.3 and 32.4 should fit the definition.

The most pragmatic approach for manufacturers, retailers and employers, as well as for control of compliance with the regulation, would be that DMG test-positive items should not be used in contact with the skin.

32.4.5 Skin Exposure Assessment

It is now possible to quantify nickel and other metals deposited onto the skin. Acid wipe sampling, finger rinsing and tape stripping are methods that have been used in occupational, clinical and experimental studies [20, 41–43]. It is also possible to visualize nickel on the skin by the DMG test [44]. Skin exposure assessments of nickel and other metals will contribute important information for risk assessment, assessment of occupational dermatitis and prevention efforts (see Chaps. 6 and 28).

32.4.6 Systemic Exposure

The role of nickel in the diet, surgical implants and dental materials remains partly controversial and is reviewed in Chaps. 17, 19 and 22.

32.5 Genetic Susceptibility

It is well known that skin exposure to nickel is the main risk factor for sensitization to nickel and nickel dermatitis. It is obvious that also endogenous factors are of importance for sensitization and allergic contact dermatitis. During recent years, efforts have been made to identify genetic factors associated with nickel allergy and nickel dermatitis. Most interest has concerned atopic dermatitis and filaggrin gene mutations.

Several studies have been performed to elucidate associations between genetic factors and nickel allergy or nickel dermatitis. A number of review articles have discussed recent developments [45–49]. Studies have been performed by various methodologies, including population-based studies among families, twins and the general population; studies in patients with atopic dermatitis, hand eczema or nickel allergy; and experimental studies in patients and animals and in vitro studies. To summarize some current positions that may be of particular relevance to clinicians:

- The prevalence of nickel sensitization is increased in patients with atopic dermatitis.
- Multiple factors affect the association between atopic dermatitis and skin sensitization.
- Filaggrin gene mutations increase the risk of atopic dermatitis and likely the risk of sensitization to nickel due to compromised chelation of nickel in the stratum corneum.
- Filaggrin null mutations have been associated with nickel allergy and self-reported jewellery dermatitis.
- Some epidemiological filaggrin studies on nickel have been stratified for piercing.
- Epigenetic regulation likely has a role in nickel dermatitis.
- Results from epidemiological studies concerning genetic predisposition to nickel allergy have sometimes been conflicting.
- More studies are needed to determine the role of genetics in the development of nickel allergy and nickel dermatitis.

Ongoing and future research is expected to contribute with further knowledge as to the role of genetic factors in nickel allergy. This may be of high relevance for diagnosis, treatment and prevention.

32.6 Potency, Cross-Reactivity and Concomitant Reactivity

It is sometimes assumed that nickel is a potent skin sensitizer, as it is a very frequent sensitizer. Based on results from predictive testing in animals by the guinea pig maximization test (GPMT) and the local lymph node assay (LLNA) in mice, however, it has been concluded that nickel is a moderate or weak sensitizer. Negative LLNA results are considered false negative, and mice have been sensitized to nickel by other test methods [50–52].

Although the sensitizing potency of nickel is moderate in animal experiments, the dose required for elicitation of nickel dermatitis in humans is very low (see “Dose-Response Studies”).

Concomitant reactivity to nickel and other metals is seen relatively often in dermatitis patients. It is generally difficult to tell if concomitant reactions to commonly occurring skin sensitizers are related to cross-reactivity, co-reactivity or increased susceptibility. Cross-challenge experiments in guinea pigs indicate cross-reactivity for nickel and palladium, but not nickel and cobalt or nickel and chromium [53–55].

Patch test results among dermatitis patients and adolescents in the general population have been analysed concerning concomitant and solitary reactivity to nickel, chromium and cobalt [19, 56, 57]. Of particular interest is that cobalt allergy without nickel allergy is relatively frequent, compared with the general assumption that cobalt allergy is coupled to nickel allergy owing to assumed concomitant exposure or

cross-reactivity. It should also be noted that cobalt often is used in other forms and products than nickel (see Chap. 28).

32.7 Clinical Picture

Skin lesions in nickel-allergic persons may be transient or more persistent, localized to skin contact with certain items, to the hands, or more widespread. When localized to the skin under jewellery, buttons, a belt buckle, spectacle frames, a wristwatch and other personal items, it may be relatively easy to identify and avoid the causative exposure. It may, however, be difficult to identify the exposure(s) causing or contributing to hand eczema.

Historically, jewellery, suspenders, hooks, zippers and buttons in clothes and spectacle frames have often been reported to cause the first noted lesion (primary eruption). During recent decades, when ear and body piercing has been increasingly popular, dermatitis from jewellery for pierced holes has been common. The picture is dependent on fashion, which varies, and to the properties of the materials used, i.e. nickel release.

Nickel-allergic individuals run an increased risk of developing hand eczema [3]. Approximately 30–40% of nickel-allergic individuals report that they ever have experienced hand eczema, compared with 15–20% among non-nickel-allergic individuals [12, 58, 59]. Patients with hand eczema and nickel allergy often have recurrent vesicular hand eczema [60]. Occupational nickel exposure should be considered in nickel-allergic patients with hand eczema. In some countries, the association between nickel allergy and hand eczema in young women may have weakened (see "Severity and Prognosis").

Systemic exposure to nickel by ingestion, implants and dental materials is reviewed in Chaps. 17, 19 and 22.

32.7.1 Severity and Prognosis

Many mild cases of nickel dermatitis will clear with avoidance of nickel exposure and with topical treatment. Hand eczema in nickel-sensitive patients has often been considered to have a poor prognosis and may in some cases be resistant to treatment and persist for years [2, 3, 61].

Severe hand eczema occurs in nickel-allergic patients, particularly in work-related cases when the exposure may be massive or difficult to avoid, and when combined with exposure to wet work and other skin irritants that impair the skin barrier function. Other well-known factors that contribute to severe symptoms or poor prognosis of nickel allergy are multiple sensitization and a history of atopic dermatitis [3, 47, 62].

Some studies among the general population indicate that the prognosis of nickel allergy has become more favourable. The association has weakened between nickel allergy and hand eczema among young women in Denmark, although not among older women, following the Danish nickel restriction of 1991 [63]. In a 20-year follow-up of patch-tested schoolgirls in Sweden, the prognosis of hand eczema in relation to nickel allergy was more favourable than previously reported [64]. The participants had, however, been patch tested with nickel and informed about any nickel allergy in the first study, and it is unknown if they had avoided nickel exposure since then.

32.8 Diagnosis and Prevention in the Clinic

32.8.1 Patch Test

Nickel sulphate 5% (2.0 mg/cm^2) in petrolatum is used in the European baseline series, while 2.5% (1.0 mg/cm^2) is used in the North American series [8, 65]. The ready-to-use patch test system TRUE Test® contains a nickel patch (0.20 mg/cm^2). Active patch test sensitization from nickel sulphate 5% in petrolatum has not been reported. The proportion of irritant and doubtful patch test reactions to nickel is low, compared with that to cobalt, chromium and most other baseline patch test substances [57, 66, 67]. Poor reproducibility of patch test reac-

tions to nickel among infants has been reported [68] (see Chap. 37).

Patch testing with serial dilutions of nickel is performed to assess an individual's degree of sensitivity or to confirm that a reaction is allergic. Patch testing with metal discs of various nickel-containing materials gives information about the ability of materials to cause allergic contact dermatitis (Chap. 6) [69–71]. Such testing is sometimes used when patients are evaluated in relation to implants (see Chap. 24).

32.8.2 Dose-Response Studies

Compilations of dose-response results give important information on elicitation thresholds [72]. Dose-response studies have been performed with serial dilutions of nickel by patch testing and repeated open application testing (ROAT) [73]. The patch test dose to which 10% of nickel-allergic individuals reacted (ED10) was 0.78 μg nickel/cm^2. The reactivity to the accumulated dose per unit area by ROAT was similar to that by patch test. Knowledge about elicitation thresholds is important for understanding that low doses of nickel are able to cause allergic contact dermatitis by prolonged contact and that nickel deposited onto the skin by short and repeated contact likewise is able to cause allergic contact dermatitis. See further Chap. 6 concerning measured levels of skin exposure to nickel in various occupations.

32.8.3 DMG Test

The DMG test presents a cheap, simple and powerful tool for prevention of nickel dermatitis by exposure reduction. All patients with nickel allergy and contact dermatitis should be encouraged to use the DMG test to minimize nickel exposure from personal items, in the workplace and during leisure. It may be necessary for the patient to get support by the occupational health service, safety representative or employer to reduce exposure in the workplace.

32.8.4 Exposure Assessment

In the case of suspected work-related nickel allergy, it may be of high importance to make a thorough assessment of the patient's exposure to nickel, other skin sensitizers and skin irritants. This is essential for diagnosis, rehabilitation and medicolegal purposes [65]. The assessment should preferably include a systematic investigation with the DMG test to identify sources of nickel exposure in the workplace. Nickel on the skin should also be assessed qualitatively by the DMG test or quantitatively if chemical analysis is available (see "Exposure" and Chap. 6).

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Metal Allergy: Palladium

33

Joris Muris and Cees J. Kleverlaan

33.1 Introduction

Palladium (Pd) was discovered by William Hyde Wollaston in 1803 and named after the asteroid Pallas. Soon, it became clear that this metal had very interesting chemical properties. It had a great ability to absorb hydrogen (up to 900 times its own volume) and was therefore used as a catalyst in many (de)hydrogenation reactions. Today, Pd chemistry is still of great interest: in 2010 the Nobel Prize in chemistry was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for Pd-catalysed cross-coupling in organic synthesis. Pd is widely used in chemical, electronic, and especially automotive industries as a catalyst [1], which taken together accounts for approximately 88.8% of the total Pd demand worldwide in 2013 (Table 33.1). Still, human exposure to Pd is mainly through contact with jewellery and dental appliances, which account for 4.0 and 5.3% of the total demand, respectively. There was demand for 15.9 tonnes of Pd for the dental industry worldwide in 2013 (Johnson & Matthey: www.platinum.matthey.com).

Table 33.1 Palladium demand in tonnes for dental industry in various areas of the world

	2004	2009	2013
Europe	2.5	2.0	2.3
Japan	16.2	9.2	6.4
USA	7.3	8.1	6.7
China	0.2	–	–
Rest of the world	0.3	0.5	0.5
Total	26.4	19.8	15.9

Source: www.platinum.matthey.com

33.2 Bioactivity of Palladium

Pd is a group 10 metal in the periodic table and has close chemical resemblance with nickel (Ni) and platinum (Pt). The latter two metals have interesting bioactive properties. The metal Ni and its alloys are known for adverse reactions, especially allergic contact dermatitis, while Pt salts are well known in cancer treatment. As expected, there is cross-reactivity between Ni and Pd for allergic contact dermatitis, and broad spectrum organometallic Pd compounds are currently being explored as a possible cancer treatment [2]. Pd exists as a pure metal, alloy, inorganic salt, and organometallic compound. The pure metal and alloy can release ions and react to inorganic salts or organometallic compounds depending on the local environment. The synthetic inorganic salts or organometallic compounds are frequently used in catalysis. Pd and its compounds have a very low to moderate threshold for acute oral toxicity: about 200 to >4000 mg kg^{-1} body weight

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depending on the solubility of the Pd compound used [3–5]. However, intravenous administration results in much higher toxicity (6 mg kg^{-1} body weight) [4].

33.3 Palladium Release

Considerable amounts of Pd are released from dental alloys in in vitro and in vivo studies [6–11]. As explained before, this release is influenced by the composition and microstructure of the alloy and the surrounding environment [11]. Pd-containing dental alloys were reported to release up to 33.7 μg/cm^2/week of metal ions in a corrosive test solution [12]. Precious dental alloys can be divided into two major groups: gold (Au)-based and Pd-based and Pd-based alloys can be subdivided into silver (Ag) and copper (Cu) alloys (Table 33.2).

Measurable levels of Pd and other components of dental alloys are found in saliva and oral mucosa cells, which is consistent with release of Pd from dental appliances [8, 13, 14]. Also, samples of serum and urine of patients with Pd monosensitization were found to have significantly elevated concentrations of Pd, with the highest in urine, suggesting a predominantly renal excretion of Pd. Amounts in serum were, however, not significant [13]. These levels were shown to return to normal values when the appliances were removed from the oral cavity, along with a remission of symptoms. Levels of released Pd from dental appliances correlated to oral clinical symptoms and to skin sensitization to Pd. Also, specific induction of IFN-γ responses in peripheral blood mononuclear cells (PBMC) was detected in Pd-sensitized individuals [13].

33.4 Adverse Reactions Towards Palladium

The first report on Pd allergy (1955) describes a 35-year-old housewife who suffered from contact dermatitis on her left fourth finger, on which she wore a 90 wt% Pd-containing wedding ring [15]. In 1969, a case of contact allergy to Pd was reported by a chemist working with noble metal salts, including $Na_{(2?)}PdCl_4$ [16]. Occupational exposure to Pd is infrequent but may also occur in dental technicians, miners, and workers in the electronics and chemical industries [1, 9, 17].

Although Pd has been used in dental alloys for almost a century [18], its wide-scale use started in the 1970s due to increasing gold prices [19]. Shortly thereafter, Pd allergies emerged in the literature more frequently [19]. The first report on Pd allergies from dental alloys was documented by two Dutch researchers, van Ketel and Nieboer [20].

Japan has long been the largest Pd-consuming region for dental applications, followed by North America and then Europe, although Japan's demand has decreased substantially in the last years (Table 33.1). Interestingly, Pd allergy prevalence seems to be distributed similarly, that is, 7–24% in Japan [21, 22], 8.5–13.3% in the USA [23–25], and 4.9 (Germany)–11.7% (Spain) [26, 27] in Western Europe. In Europe, much more data is available, and there are considerable variations between Northern and Southern European

Table 33.2 Sub-classification of the Pd-based dental alloys based on weight percentage according to the American Dental Association (ADA)

Classification	Percentage of noble metals	Subgroups	Most important components
High-noble	≥60% Au + Pt + Pd (>40% Au)	Au-based alloys	Au-Pt Au-Pd
		Pd-based alloys	Pd-Au (>40Au)
Noble	≥25% Au + Pt + Pd	Pd-based alloys	Pd-Au (<40Au) Pd-Ag Pd-Cu
		Ag-based alloys	Ag-Pd

countries [17]. Several extensive studies (including between 542 and 4446 patients) described the difference in prevalence between gender in dermatitis patients: 17.1% vs. 3.1% in Spain; 14.8% vs. 2.5% in Turkey; 14.9% vs. 3.2% in Minnesota, USA; and 6.7% vs. 2.3% in Italy for women and men, respectively [26, 28–30]. Most reports on Pd allergy are related to dental alloys and oral disease [20, 31–44]. This clearly shows the importance of dental alloys as the main source of exposure.

Until the introduction of a new test allergen for use in patch testing, the prevalence of Pd monosensitization ranged from 0.2% [17] to 1.6%, while the prevalence of Pd sensitization in association with Ni sensitization was 13.0% [13]. The salt normally used in epicutaneous patch testing for diagnosis of Pd allergy was, until 2007, Pd chloride, $PdCl_2$ (1–2% in petrolatum or in water), which forms an oligomeric or polygomeric structure with water, accounting for a very poor solubility of this salt. As such, skin penetration, of which epicutaneous patch testing highly depends, might be impaired and thus results in false negatives. Sodium tetrachloropalladate, Na_2PdCl_4, at 3%, was shown to be a much more accurate test allergen for epicutaneous patch testing, mainly due to its solubility in water and monomeric structure [45–47]. In fact, the results of patch testing with this new test salt showed much higher rates of Pd sensitization, which meant that previously Pd sensitization possibly had been largely underestimated (Fig. 33.1). A multicentre study in Europe, where 3% Na_2PdCl_4 was used, showed that prevalence of Pd monosensitization increased from 1.6% to 4.2% and that Pd sensitization prevalence increased from 9.3% to 18.2% among dermatitis patients [48]. Interestingly, the rate of Pd sensitization was similar to that of Ni (6–7%) [49]. Furthermore, the results of that study support the previous suggestion [50] that Pd might be a more potent sensitizer than Ni, since a formulation of the new Pd salt including fewer atoms was sufficient for elicitation and likely also sensitization [51].

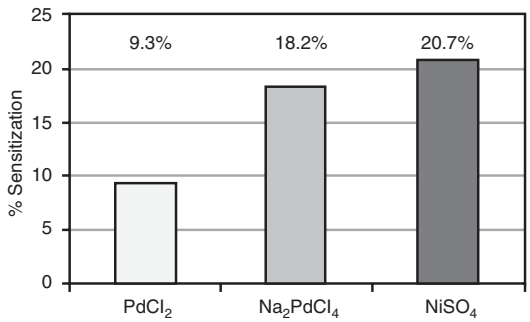

Fig. 33.1 Positive skin test results (+, ++, and +++) to 1% or 2% $PdCl_2$, 3% Na_2PdCl_4, and 5% $NiSO_4$ from a multicentre study in Europe among 1651 dermatitis patients (Data adapted from [48])

In contrast with that of Ni, Pd (mono)sensitization is not related to female sex, which relates to the different sources of exposure of the two metals [49]. The prevalence of Pd allergy is higher in female patients, because it goes together with the prevalence of Ni sensitization, which is higher in women and which relates to the contact with jewellery. Thus, different sources of exposure are expected.

Although most Pd allergy cases are related to dental alloys, a few describe clinically relevant allergic contact dermatitis to Pd [15, 16, 52, 53]. Several authors have described Pd-induced sarcoidal-type allergic contact granulomas due to body piercings [33, 54–59]. Some have discussed the relevant systemic allergic contact dermatitis to dental Pd [21, 34, 40, 60, 61]. Notably, a recent report described allergic contact gastritis due to a Pd-containing dental bridge [38]. It must be stated that patients who are allergic to Pd rarely exhibit a reaction to skin exposure to the metal [17, 62].

Despite the numerous case reports describing adverse reactions to Pd-containing dental alloys, the clinical relevance of positive patch tests to Pd is still unclear, or at least difficult to assess. One of the reasons is that the clinical picture of Pd-induced allergic contact stomatitis is ambiguous. Furthermore, it's possible that no oral lesions may be present in the case of systemic contact allergy to dental materials, as pointed out in several case reports; instead, systemic complaints or lesions could be atypical, e.g. gastritis or alopecia. Pd sensitization, as measured by positive patch tests, is frequently found in the absence of clinical relevance, both intra- and extra-orally.

Case reports showed that strongly palladium-sensitized individual appeared to have relatively mild contract dermatitis reactions [62, 63]. Furthermore, Pd allergic patients' lack of awareness of the presence of dental alloys and/or their composition complicates the evaluation of clinical relevance considerably.

Pd allergies have been estimated to be overall equally prevalent in dermatitis and oral disease patients at 7–8% (range < 1 up to 24% worldwide) [17, 21]. However, this figure is based on studies that have evaluated either dermatitis or oral disease patients. Therefore, interregional, interindividual, and inter-laboratory variation, as well as test materials used, the number of patients, and the period of testing, could skew these observations. Moreover, some investigators marked a 2+ reaction as positive, while others scored a 1+ reaction as positive, and patch test readings were done at various different time points and frequencies. Finally, because Pd is not included in standard patch test series but is rather part of specific 'metal', 'oral disease', or 'dental' screening series, it is not always clear what specific patients have been tested. Studies that compare the prevalence of dermatitis and oral disease patients are scarce, but they do indicate a higher prevalence among patients with oral disease relative to those with dermatitis. One study reported that, among 106 Pd-sensitized patients, 55.7% suffered from oral disease and 29.2% from allergic contact dermatitis [29]. An older study retrospectively comparing patients with intra-oral complaints (n = 397) to patients suffering from eczema (n = 112) showed that especially gold and Pd sensitivity were significantly increased in the dental patient group: 23% vs. 6% for gold and 8% vs. <1% for Pd [64]. Another important issue to address in this context is the cross-reactivity between nickel and Pd.

33.4.1 Cross-Reactivity to Nickel and Concomitant Reactivity to Other Metals

The relevance of a positive patch test reaction to Pd is likely compromised by potential cross-reactions to nickel, even though exclusive positive reactions to Pd are also reported continuously and appear to be more prevalent in recent years [17]. The simultaneous positive reactions of nickel and Pd are explained by (1) sensitization to both metals, (2) contamination of the Pd patch test material with traces of nickel (despite the fact that several studies have disproved this theory) [50], and (3) the fact that nickel and Pd have similar chemistry and electron arrangements, which could cause cross-reactivity at the T-cell level [65, 66]. It has also been shown that nickel and Pd form similar complexes with sulphur ligands [67], which may explain why both metals form similar metal-protein complexes as suggested by Santucci [68]. Hindsén et al. [69] provided in vivo evidence for cross-reactivity to nickel and Pd by systemic administration. They produced flare-up reactions on sites previously patch tested with nickel and Pd after oral exposure to nickel. In this study, contamination was excluded by chemical analysis.

Other metals often produce positive patch test results in Pd-sensitized patients. In Spain, researchers found concomitant reactivity to nickel (97%), cobalt (36%), and chromium (13%) [26]. These figures are similar to findings in Austria [70]. In the USA, the instance of co-sensitization to nickel was considerably less (57.0%) and was strikingly only slightly higher than that for gold (48.2%) [29]. In the latter report, co-sensitization to cobalt and chromium was measured at 37.6% and 10.2%, respectively.

33.4.2 Palladium-Induced Immune Responses

Since palladium exposure is mainly due to dental applications, exposure is mainly to the oral mucosa. Clinically, this can result in, for example, non-plaque-related gingivitis (Fig. 33.2). Even though an association was evident, in many cases, this was not always reflected by a systemic Pd-induced immune response. Apparently, not all cases of non-plaque-related gingivitis are caused by allergic pathways (Th-1 or Th-2), but rather a local innate immune response may be responsi-

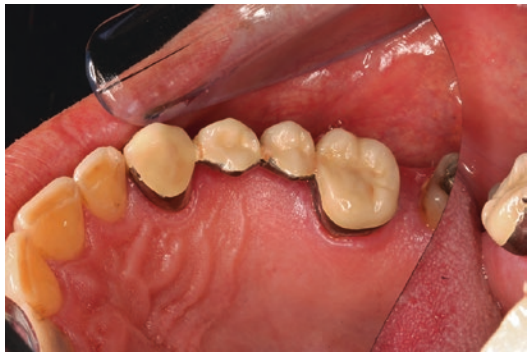

Fig. 33.2 An example of non-plaque-related gingivitis around the metal bridge

ble for the inflammation. In the human body, both Ni and Pd can directly activate the innate immune system through toll-like receptor 4 (TLR-4) [71]. This means that non-plaque-related gingivitis does not necessarily result from allergy but could simply be an innate immune response, functioning much the same way as irritant contact dermatitis/stomatitis. Innate effects were investigated by using in vitro cultures based on human monocyte-derived dendritic cells (MoDC) and THP-1 cells [72]. These cells were exposed to different metals, with and without an endotoxin (lipopolysaccharide; LPS). IL-8 production was used as a parameter for innate stimulation. The results showed that Pd and Au of the dental alloys, and especially PdCu alloys, can trigger the innate immune response. In these experiments, the innate immune response was enhanced when bacterial endotoxins, like LPS, were added to the medium.

Systemic effects of Pd were investigated in well-defined positive and negative control patients using patch test results from testing with Na_2PdCl_4 and $NiSO_4$ as the gold sttandard [73]. A lymphocyte proliferation test (LPT) and specific cytokine production profiles (Th1, IFN-γ; Th2, IL-5 and IL-13) were used to investigate the systemic effect measured by using peripheral blood mononuclear cells (PBMCs). It was found that, in contrast to IFN-γ (Th1), the Ni- and Pd-induced production of Th2 cytokines (IL-5 and IL-13) were good predictors for sensitization based on patch testing. Although the findings with regard to Th2 cytokines correspond to results of Minang et al. [74], they were in conflict with previous research that showed predominant Th1 responses in Ni-allergic patients. Pd-induced LPT showed good specificity (95%), meaning that only very few false-positive results were obtained. However, it lacked sensitivity (63%), meaning that several false-negative results were found. High specificity is especially useful in cases of a positive patch test with unclear clinical relevance. Pd-induced LPT was found to be strongly related to present exposure to Pd (e.g. the presence of Pd-based dental alloys), clinical anomalies, and even subjective complaints [75]. In cases of sensitization in the absence of exposure, the LPT is more likely to be negative. LPT could therefore be useful to differentiate between clinically relevant patch test results and irrelevant ones. Finally, positive LPT results could (further) support an indication for invasive dental replacement treatment in tricky cases.

Ultimately, the so-called 'irrelevant' positive patch test results still have some relevance, since it is clear that patients with positive patch test results to metals, regardless of possible clinical relevance, should not receive dental appliances containing these metals. It is also important to realize that a negative patch test result to a specific metal does not guarantee the ability to safely use that metal on a patient in the future, because the patient may not have been previously exposed; an allergy could still develop after patch testing. For the dermatologist and the general dental practitioner, it is important to realize that dental alloys are possible sources of metal exposure that may contribute to (metal-induced) skin disease, even in the absence of oral lesions.

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Metal Allergy: Titanium

34

Curt Hamann

34.1 Introduction

Titanium (Ti, atomic number 22) is a silver-white transitional (reactive) metal first discovered in Cornwall in 1791. This extremely strong metal was aptly named after the Titans of Greek mythology who were considered the embodiment of strength. Despite its early discovery and its being the ninth most abundant element on earth, titanium was not isolated until 1910, and a viable commercial extraction process was not developed until 1938. Titanium is relatively difficult and hence expensive to extract, but its properties—high resistance to corrosion, high biocompatibility, low specific gravity, high specific strength, and nonmagnetic—have made it highly desirable for a number of specialized applications, first in aerospace and military applications followed by food, pharmaceuticals, and cosmetics.

These same properties, coupled with its inherent capacity for osseointegration, have made titanium a favorite choice for medical and dental implants, and related publications from dentistry and medicine have increased exponentially since the 1970s [1]. The reputation of titanium as biologically inert and therefore nonallergenic has been and remains strong. Indeed, titanium was not even among the 35 metals covered in a 1999 text devoted to the topical effects of metals and their systemic absorption by the skin [2]. Titanium has been touted as the ideal material for dental and surgical implants, especially for patients who are hypersensitive to other conventional metals, for whom it may indeed be the safest choice [3–7].

Yet even while the statement that titanium was "fully inert" was being made in the mid-1990s [4], titanium had already been implicated in hypersensitivity reactions since the 1980s, and its role in implant failure had been questioned since the early 1990s. Admittedly, allergic reactions to titanium are rare. Their occurrence in relation to medical and dental implants, however, raises concerns. Despite titanium's resistance to corrosion, ample evidence has shown that, like any metal, it is not completely inert. In the human body, titanium implants are subjected to mechanical and chemical stresses that can lead to physicochemical corrosion that could be involved with implant loosening or failure. Corrosion also leads to the release of ions and oxides that may combine with proteins to become haptens. This process may increase an individual's risk of becoming hypersensitive to titanium. Furthermore, the proportion of the population exposed to medical and dental implants, many of which will incorporate titanium because of its exceptionally beneficial profile, will increase as the population ages.

To further understanding of this unquestionably increasingly important metal, this chapter

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(1) reviews the sources and properties of titanium and its alloys, (2) evaluates the efficacy of methods used to diagnose titanium allergies, and (3) discusses the implications of the evidence for titanium allergies related specifically to dental and medical devices. The mechanisms underlying metal hypersensitivity are discussed elsewhere in this text.

34.2 Titanium and Its Alloys and Their Uses

Most titanium ore (95%) is refined into titanium dioxide (TiO_2). Globally, each year 4 million tons of TiO_2 are used as a whitener in products ranging from paint, ink, food, cosmetics, pharmaceuticals, plastics, paper, candy, and toothpaste [8]. The remaining 5% of titanium ore is refined to metal [9].

Because of its immediate reactivity with oxygen, metallic titanium does not exist in nature; rather, it exists in three mineral forms of titanium dioxide: rutile, anatase, and brookite. Anatase has the greatest chemical reactivity, which is thought to result from the large facet size of its crystals and which is potentially associated with increased toxicity [10]. In addition to distinct crystalline structures, TiO_2 particles are divided into two size distributions: TiO_2FP (fine particles, 100–2500 nanometers) and TiO_2NP (nanoparticles, 1–100 nanometers). The smaller the particle size is, the larger is the surface area, which increases catalytic activity and likely also influences bioreactivity.

From the perspective of materials science, titanium and its alloys are classified into types based on their metal content and crystalline structures. Hexagonal close-packed crystalline-structured alloys are termed alpha types, while body-centered cubic crystalline-structured alloys are termed beta types. Different stabilizing elements increase or decrease the temperature at which alpha structures phase shift to beta structures (Table 34.1). Alpha stabilizing elements, which include aluminum (Al), tin (Sn), gallium (Ga), zirconium (Zr), carbon (C), oxygen (O), and nitrogen (N), contribute to increased high-temperature performance of alloys in combustion engine applications and to other properties such

Table 34.1 Types of titanium and their stabilizing elements [11, 26, 135, 136]

Type (stabilizing element)	Typical materials[a]
α and near α (Al, Sn, Ga, Zr, C, O, N)	Commercially pure Ti (Grades I–IV)
	Ti-5Al-2.5Sn
	Ti-5Al-6Sn-2Zr-1Mo
	Ti-6Al-2Sn-4Zr-2Mo
	Ti-8Al-1Mo-1V
$\alpha + \beta$	Ti-5Al-2.5-Fe
	Ti-5Al-2Mo-2Fe
	Ti-5Al-3Mo-4Zr
	Ti-5Al-2.5Fe
	Ti-6Al-7Nb
	Ti-6AL-4V (ELI)
	Ti-6Al-4V (Ti6-4)
	Ti-6Al-6V-2Sn
	Ti-6Al-2Sn-4Zr-6Mo
	Ti-15Zr-4Nb-2-Ta-0.2Pd
near β and β (V, Mo, Nb, Ta, Cr)	Ti-3Al-8V-6Cr-4Mo-4Zr
	Ti-4.5Al-3V-2Mo-2Fe
	Ti-5Al-2Sn-2Zr-4Mo-4Cr
	Ti-6Al-6Fe-3Al
	Ti-10V-2Fe-3Al
	Ti-13V-11Cr-3Al
	Ti-15V-3Cr-3Al-3Sn
	Ti-35V-15Cr
	Ti-8Mo-8V-2Fe-3Sn
	Ti-11.5Mo-6Zr-4.5Sn
	Ti-15Mo
	Ti-30Mo,Ti-40Mo
	Ti-13Nb-13Zr
	Ti-16Nb-13Ta-4Mo
	Ti-29Nb-13Ta
	Ti-29Nb-13Ta-2Sn
	Ti-29Nb-13Ta-6Sn
	Ti-29Nb-13Ta-4.6Zr
	Ti-29Nb-13Ta-7Zr
	Ti-25Pd-5Cr
	Ti-20Cr-0.2Sn
	Ti-15Sn-4Nb-2Ta-0.2Pd
	Ti-15Sn-4Nb-2Ta-0.2Pd-0.2O
	Ti-30Ta
	Ti-5Zr
	Ti-10Zr
	Ti-10Zr-5Nb-5Ta (ARB processed)[c]
	Ti-15Zr (Roxolid®)
	Ti-15Zr-10Cr
	Ti-15Zr-4Nb-4Ta-0.2Pd
	Ti-15Zr-4Nb-4Ta-0.2Pd-0.2O-0.05 N
	Ti-19Zr-10Nb-1Fe

[a]Numbers represent percentage of element present in alloy
[b]*ELI* extra low interstitial
[c]*ARB* accumulative role bonding

as weldability and machinability. Beta stabilizing elements include vanadium (V), molybdenum (Mo), niobium (Nb), tantalum (Ta), and chromium (Cr), which improve the room temperature strength of alloys. There are also hybrid alloys, which contain both alpha and beta stabilizing elements. Hybrid alloys are further subdivided into near alpha, alpha + beta, and near beta. Both alpha and beta types also may contain iron (Fe), copper (Cu), nickel (Ni), silicon (Si), and boron (B), which are added to modify physical and chemical properties.

Titanium and its alloys are also classified by grade, a numbering system used to identify the ASTM (American Society for Testing and Materials) standard that applies to each alloy. In 2015 Wood and Warshaw provided an extensive tabulation of many industrial and medical grades of titanium [11]. The first four grades and grade 7, which are classified as commercially pure titanium (CpTi), are unalloyed. Their purity ranges from 99.0% to 99.5%, and their oxygen content from low to extra high as the grade increases. The remaining grades are alloys in which titanium is combined with various percentages of a variety of other elements such as palladium, ruthenium, nickel, molybdenum, gallium, tantalum, vanadium, aluminum, tin, zirconium, chromium, iron, niobium, and silicon. The formulations are designed for specific purposes, depending on the desired property or combination of properties such as ductility, strength, hardness, electric resistivity, creep resistance, and resistance to corrosion from a specific media.

The first-generation biomedical implants, which were used between 1950 and 1990, were commercially pure alpha or mixed alpha and beta alloys. Since 1990 second-generation biomedical implants have primarily been manufactured from beta alloys [12]. Consequently, clinicians could easily encounter patients with implants of either type. The most common grades used in implantable devices are found in Table 34.2.

Grade 2 CpTi (purity, 99.2%; oxygen content, medium) is notable because it is often used for dental and medical implants. Grade 4 CpTi (purity, 99%; oxygen content, extra high) is also used in some dental implants. Grade 5, Ti-6Al-4V (i.e., alloyed with 6% aluminum, 4% vanadium, a maximum of 0.25% iron, and a maximum of 0.2% oxygen), is one of the workhorses of titanium alloys accounting for about half of total titanium alloy usage [13]. Lightweight but strong while highly resistant to corrosion, it has been a favorite of the aerospace, marine, and chemical processing industries.

Although grade 5 is stronger than pure titanium grades, its surface wear properties can be relatively poor in certain loading situations, and the alloy can corrode. Surface treatments such as nitriding and oxidizing improve its surface wear properties [14–16]. Yet, vanadium has been shown to accumulate in organs such as the bone, liver, and kidneys in implant patients. Furthermore, vanadium is cytotoxic—so much so that some vanadium compounds are considered promising treatments for cancer [17]. Vanadium also may be a type IV allergen [18, 19]. Consequently, the suitability of grade 5 Ti for permanent implants was questioned. In response to these concerns, Ti-7Nb (6% aluminum and 7% niobium) was developed as a biomedical replacement with niobium used as a substitute for vanadium [20]. This alloy has been used in hip implants since 1986.

Grade 23 Ti, or Ti-6Al-4V ELI, which has a higher purity than Ti-6AL-4V, is another option for dental and medical implants. It is suitable in applications that call for high strength, light weight, good resistance to corrosion, and durability. Its ability to tolerate mechanical and chemical damage is superior to that of the other alloys. It has been used in orthopedic pins, screws, and cables; joint replacement devices; bone fixation devices; ligature clips and surgical staples; springs; and orthodontic appliances.

Ti nitride (TiN), Ti niobium nitride (TiNbN), and Ti carbon nitride (TICN), which are extremely hard ceramic materials, also are used in medical devices, notably in surface coatings of newer hip, knee, and dental prostheses; stents; and pacemaker leads [21–25]. They are used as a top-layer coating that helps resist corrosion of articulating surfaces and retain sharp edges, for example, in scalpel or orthopedic bone saw blades. Because the color of TiN is gold, it is also used in costume jewelry.

Table 34.2 Common titanium alloys used in medical and dental devices

Grade or name	Chemical formula	Applications
2	Commercially pure, 99.2%	Medical and dental implants
4	Commercially pure, 99%	Dental implants
5	Ti-6Al-4V	Medical implants, especially artificial hip joints (many discontinued)
		Endosseous dental implants
23	Ti-6AL-4V ELI	Endosseous dental implants
		Orthopedic pins, screws, cables
		Joint replacements
		Bone fixation devices
		Ligature clips, surgical staples
		Springs
		Orthodontic appliances
29	Ti-6Al-7Nb	Endosseous dental implants
		Hip implants
None	Ti-15Mo-5Zr-3Al	Hip joints
None	Ti-6Al-2Nb-1Ta-0-8Mo	Hip joints
Ti nitride	TiN	Coatings on neurovascular stents and filters
		Prosthetic implants (especially hip)
		Surgical instruments
Ti niobium nitride	TiNbN	Coating on implants
Nitinol	55% Ni, 45% Ti	Endovascular stents, endografts, septal occluders, filters (luminal shields), cardiac pacemakers, implantable cardioverters/defibrillators
		Orthodontic appliances such as archwires
		Bone suture wires and staples
		Temporary implantable nitinol devices to relieve lower urinary tract symptoms
		Contraceptive device
	CuNiTi	Orthodontic archwires

Nitinol is an alloy composed of about 55% nickel and 45% titanium (with traces of chromium). It was developed by the US Navy, from which its name is derived (Nickel-Titanium Naval Ordnance Laboratory). Its unique property of shape memory or reversible deformation (i.e., recovers its original shape after load is removed) made it desirable for applications in a variety of industries such as dental, medical, optical (eyeglass frames), sporting goods, and aerospace. The addition of copper to a nickel titanium alloy increases resistance to permanent deformation compared to NiTi alone [26]. This combination increases the utility of the alloy when more consistent force is required, for example, to move maloccluded teeth with orthodontic treatment [27].

When electropolished, nitinol forms a stable protective TiO_2 layer that acts as an effective and self-healing barrier against ion exchange. That nitinol releases nickel at a slower pace than stainless steel also made it attractive for use in medical devices, the first of which was introduced in the late 1970s. These early devices were made without electropolishing, and corrosion was observed. Es-Souni and coworkers comprehensively reviewed the corrosion, cytotoxicity, biocompatibility, and nickel release but without discussing the simultaneous potential for concomitant Ti release [28].

The use of nitinol is now widespread. It can be found in endovascular devices such as stents, endografts, septal occluders, filters (luminal shields), cardiac pacemakers, and implantable

cardioverter/defibrillators (ICD); dental implants and appliances such as orthodontic archwires; bone suture wires and staples; cochlear implant electrodes; temporary implantable nitinol devices (TIND) to relieve lower urinary tract symptoms (LUTS) related to benign prostatic hypertrophy; Filshie® clips for tubal ligation; superelastic springs for the treatment of craniosynostosis; biopsy site markers; and radiation seed capsules for treatment of prostate and other cancers [29].

In 2002 a nitinol contraceptive device for implantation in the fallopian tubes was introduced. As a result of postmarketing reports of adverse events, including systemic allergic contact dermatitis (ACD), the US Food and Drug Administration (FDA) issued a black box warning in 2016. The warning includes the risk of metal sensitization following placement that could result in the need for removal of the device. Clinical trials for a nitinol intrauterine device (IUD) are currently underway and are thought to be promising.

The number of titanium alloys with dental and medical applications continues to increase steadily as inventors and manufacturers seek proprietary physicochemical attributes. A majority are beta or near beta formulations (Tables 34.1 and 34.2). Titanium is also used in dental and medical instruments, which can withstand repeated sterilization without compromise of cutting edges, and in vascular guidewires, heart valves, wheelchairs, crutches, and external prosthetic devices.

34.3 Properties of Titanium

Titanium is considered a highly biocompatible metal for several reasons: its resistance to corrosion from bodily fluids, bio-inertness, capacity for osseointegration, and high fatigue limit. Titanium's ability to withstand the harsh bodily environment is a result of the nonporous protective film that naturally forms on the surface of the metal in the presence of oxygen. This process, known as passivation, begins within milliseconds of the metal being exposed to the atmosphere. Within 1 s, a surface oxide film 2- to 7-nm thick is formed. The layer is strongly adhered, insoluble, and chemically impermeable. The film effectively prevents further oxidation between the metal and the surrounding environment. Furthermore, if the layer is disrupted, the exposed metallic substrate rapidly self-heals or repassivates. This capability underlies titanium's resistance to corrosion [30]. The integrity of the oxide layer, however, can be affected by wear. In an in vitro study, for example, corrosion reduced the hardness of the surface oxides in several titanium alloys, including Ti-6Al-4V, especially in the presence of proteins [31].

Titanium's capacity for osseointegration is another feature that has made it highly attractive for orthopedic and dental implants. Its inherent ability to fuse to bone, which has been recognized since 1940, confers a distinct advantage compared to the less durable fixation associated with adhesives (which can also be allergens) [32, 33]. Titanium's capacity for osseointegration reflects an interaction between the surface characteristics of the material and living tissue. Critical to the process of osseointegration is angiogenesis, which is necessary for vascularization at the interface between an implant and adjacent tissue. Without vascularization, a fibrous capsule forms around an implant that can result in loosening and eventual failure of an implant. Although the mechanism is poorly understood, both the surface microstructure and surface energy of titanium appear to enhance angiogenesis by modulating secretion of angiogenic growth factors by osteoblasts, at least partially through signaling of the $\alpha_2\beta_1$ integrin [34].

Besides relatively low wear resistance and resultant dissolution of metal ions from local corrosion reactions, the first-generation titanium implants (CpTi, alpha type and Ti-6Al-V4, alpha + beta type) were also relatively stiff (high Young's modulus) compared to bone tissue. In comparison, the mechanical (reduced Young's modulus) and chemical properties (passive film properties) of second-generation beta alloys such as Ti-(40–45)Nb were considerably improved. Although severe surface treatments have been found to affect the passive film properties, resistance to corrosion does not deteriorate. These

features make Ti-(40–45)Nb a promising material for the development of new implants [35]. Ongoing progress in materials science related to medical and dental implants highlights the need for careful reporting of device constituents.

Finally, titanium is nonferromagnetic. This feature is important from a medical perspective because it safely allows individuals with implants to undergo magnetic resonance imaging.

Despite these favorable theoretical properties, which have led to the widespread use of titanium alloys in medical and dental products, evidence of wear, corrosion, and ion release in vitro and in vivo is a harbinger of the possible risks of immunologic complications. Corrosion of implant metals primarily manifests with pitting and crevices, fretting, cracking, delamination, and galvanism [36, 37]. Wear and corrosion may result in the buildup of titanium ions and oxide metallic particulates in adjacent tissue [38–40]. In vitro studies have shown that titanium ions are released from Ti grade 2, Ti-6Al-4V, Ti-6Al-7Nb, and Ti-15Zr-4Nb-4Ta when immersed individually in eight different media and incubated for 7 days. The highest Ti release was in solutions of L-cysteine and lactic acid [41], and release increased as pH decreased [42]. Similarly, Ti release has been reported in other in vitro studies [43–49]. The release of Ti ions from implants has also been identified in animal models [50, 51]. Perhaps more importantly from an immunological perspective is the finding of elevated concentrations of titanium in serum after the implantation of many kinds of devices, including hip, knee, spinal fusion, external and internal fixation, and dental prostheses [52–60]. In contrast, however, other studies of titanium concentrations after the placement of spinal fusion instrumentation and maxillofacial miniplates have failed to find a statistically significant increase in ion release [58, 61]. Fage and coworkers recently summarized extensive evidence from in vivo and in vitro reports of corrosion and release of titanium [62]. Decreased pH, exposure to fluoride and increased temperature also may contribute to corrosion [41, 63, 64].

Titanium transport studies have shown that 99.8% of Ti is bound to transferrin [57]. Titanium preferentially binds to the N-lobe of transferrin, which may provide entry of Ti into cells via transferrin receptors [65]. Water-soluble Ti(IV) citrate and Ti(IV) nitrilotriacetate are stable in physiological conditions; yet, only the Ti(IV) citrate binds with transferrin. This is likely due to the greater stability of the Ti(IV) nitrilotriacetate compared with Ti(IV) citrate [66]. Physiologic ligands, including citrate and lactate, form water-soluble Ti(IV) complexes that may be an intermediate step between ion release from an implant and subsequent binding with transferrin. Transport of these Ti complexes may explain the presence of Ti in widespread tissues and organs, including the lymph nodes in some implant patients [39, 40, 67, 68]. Nanoparticles of titanium dioxide also combine with albumin and may contribute to the dissemination of implant corrosion debris [69]. Increased DNA damage by TiO_2 nanoparticles appears to be mediated by toll-like receptor 4 (TLR 4) with overexpression increasing the uptake through cell surfaces into the cytoplasm [70]. Whether serum albumin and transferrin-bound Ti or serum-soluble ionic Ti ligand complexes have a role in bioavailability of Ti for haptenization and antigen-presenting cell sensitization and elicitation mechanisms is unknown.

34.4 Diagnostic Options for Determining Titanium Sensitization

The efficacy of patch testing for titanium is controversial—a situation that may primarily reflect the properties of the patch testing substances and variable techniques that have been used. In terms of patients with medical or dental implants, the timing of patch testing, before or after the implant, has also been questioned. Guidelines have been proposed and may be meaningful for the detection of relevant allergies to Ni, Co, and Cr; without standardized efficacious patch test preparations for titanium, however, patch testing to determine sensitization to titanium will likely continue to be largely unhelpful [71]. In vivo diagnostic test preparations can be obtained from

manufacturers and compounding pharmacies in the United States, Europe, and Japan. In vitro diagnostic tests are offered by several specialized laboratories in the United States and Europe, but concerns about their sensitivity and specificity also exist.

34.4.1 The Elusive Optimal Patch Test Formulation

Although titanium is not included in major series such as the European Baseline Series, the Core Series of the American Contact Dermatitis Society, or the standard series of the North American Contact Dermatitis Group, various formulations of the metal have been tested in special metal or prosthetic series or in cases suspected of having a titanium allergy. For example, in a large patch test series of metal allergens, the Mayo Clinic patch tested with 1% titanium dioxide and 10% titanium in petrolatum as well as with an unspecified titanium alloy disc [72]. In an earlier study from Mayo of patients referred for patch testing related to a medical device, patients were patch tested with a disc of the exact alloy provided by the manufacturer of the device [73]. The concentration of Ti ions or TiO_2 released from the surface of manufacturer-supplied Ti discs when placed on the skin for 48 h is unknown. Not surprisingly, testing with disparate titanium compounds and metallic discs worldwide has usually been associated with negative or equivocal results. Undoubtedly, irritant, doubtful, or negative patch test reactions to titanium in case reports and prospective studies have contributed to the controversy about the sensitizing potential of titanium and reinforced the common bias that it is not an allergen.

Wood and Warshaw as well as Fage and colleagues have summarized the clinical results of patch testing reported in the literature (Table 34.3) [11, 62]. By far, titanium dioxide (whether compounded using the more reactive anatase or less reactive rutile is often unknown or not reported) in petrolatum has been the most commonly reported patch test preparation (Fig. 34.1). However, very few positive patch reactions to TiO_2 have been reported [74]. Overwhelmingly the use of TiO_2 for patch testing has been associated with negative reactions, which would be predicted by its physicochemical properties as discussed below. The few reported positive reactions could have been irritant reactions related to a high or low pH of the patch test preparations depending on how it was manufactured or a true-positive reaction due to another metal contaminant.

Fage et al. reviewed titanium penetration in animal and human studies that were primarily performed to demonstrate the remarkable safety profile of topically applied medicaments, cosmetics, and sunscreens containing TiO_2 [62]. In one study, for example, sunscreen with titanium dioxide was applied to the volar arm, which was then tape stripped. The distribution of titanium dioxide particles was analyzed spectroscopically. Even after repeated applications of the sunscreen, no microparticles were found in the deep layers of the stratum corneum. Based on histological investigation of the tape-stripped areas, less than 1% of the applied TiO_2 was found in a given follicle, and no penetration of titanium dioxide into viable skin tissue could be detected [75]. How a water-insoluble oxide of titanium that does not penetrate the skin and is safely used in millions of tons of topically applied products each year became the leading choice for patch testing to detect titanium sensitization from an implanted metallic prosthesis is unclear.

Yet the proliferation of reports of negative patch test reactions to TiO_2 in patients with a failed surgical or dental implant, combined with prospective studies that support those negative results, has reinforced the consensus view that an allergy to titanium cannot be the underlying cause. Not surprisingly, no other water-insoluble metallic oxide that cannot penetrate the stratum corneum is routinely used as the preferred patch test substance to diagnose patients with other suspected metal allergies. On the contrary, the selection of a water-soluble salt for the common metals that penetrate the skin benefited from extensive dose-response studies conducted with different salts, concentrations, and excipients in sensitized patients before a consensus began to emerge. When the ability of a substance to penetrate the

Table 34.3 Summary of titanium compounds used in patch testing

Ti compound	Chemical formula[a]	Molar mass (g/mol)[a]	% Ti (w/w)[a]	Form	Color	Solubility in water and stability in air and water
Titanium (metal)	Ti	47.9	100	Solid	Silvery	Reacts slowly with air/water at ambient conditions, which inhibits further oxidation
Titanium(II) oxide	TiO	63.9	75	Solid	Bronze	Unstable, and readily oxidizes in air
Titanium(III) oxide	Ti_2O_3	143.7	66.6	Solid	Violet/black	Unstable, and readily oxidizes in air to TiO_2
Titanium(IV) oxide	TiO_2	79.9	59.9	Solid	White	Stable, but insoluble in water
Titanium(III) nitride	TiN	61.9	77.4	Solid	Golden	Stable, but insoluble in water
Titanium(IV) carbide	TiC	59.9	79.9	Solid	Gray/black	Stable, but insoluble in water
Calcium titanate(IV)	$CaTiO_3$	135.9	35.2	Solid	White	Stable, but insoluble in water
Titanium(III) chloride	$TICl_3$	154.2	31	Solid	Red/white	Soluble in water but oxidizes to form a precipitate
Titanium(IV) chloride	$TiCl_4$	189.7	25.2	Liquid	Colorless	Soluble in water but decomposes to TiO_2 and HCl fume
Titanium(IV) sulfate	$Ti(SO_4)_2$	240	20	Solid	Colorless	Soluble in water, but hydrolyzes
Titanium(V) isopropoxide	$TiC_{12}H_{28}O_4$	284.2	16.8	Liquid	Colorless	Rapidly decomposes in water to produce TiO_2
Titanium(III) oxalate (anhydrous)	$Ti_2C_6O_{12}$[a]	359.8	26.6	Solid	Yellow/brown	Prone to oxidation in air, and sparingly soluble in water
Titanium(IV) oxalate (anhydrous)	TiC_4O_8[a]	223.9	21.4	Solid	Off-white	Stable, and very slightly soluble in water
Ammonium titanium(IV) oxide oxalate (anhydrous)	$TiC_4H_8N_2O_9$[a]	276	17.3	Solid	White	Stable, and freely soluble in water
Potassium titanium(IV) oxide oxalate (anhydrous)	$TiC_4K_2O_9$[a]	318.1	15.1	Solid	White	Stable, and soluble in water
Ammonium titanium(IV) peroxo citrate (anhydrous)	$Ti_2C_{12}H_{24}N_4O_{18}$	608.1	15.7	Solid	Light yellow	Stable, and very soluble in water
Titanium(IV) lactate ammonium hydroxide	$TiC_6H_{18}N_2O_8$	294.1	16.3	Liquid	Colorless	Stable as a clear aqueous solution (approx. 50%)
Titanium(IV) lactate tetramethylammonium hydroxide	$TiC_{14}H_{34}N_2O_8$	406.3	11.8	Solid	Off-white	Stable as a pearly white aqueous solution (approx. 40%)
Titanium peroxide	H_4O_4Ti[b]	115.9	41.3	Solid	NA	Stable but insoluble in water
Titanium salicylate	$C_{28}H_{20}O_{12}Ti$[b]	596.3	8.0	Solid	White	Stable, and slightly soluble in water
Titanium tannate	$Ti(C_{76}H_{48}O_{46})$[b]	174.5	2.7	Solid	Yellow	Stable, but insoluble in water

[a]Chemical formula, molar mass, and % titanium listed for compounds on the anhydrous basis
[b]As reported by Wood and Warshaw [11] but author could not confirm

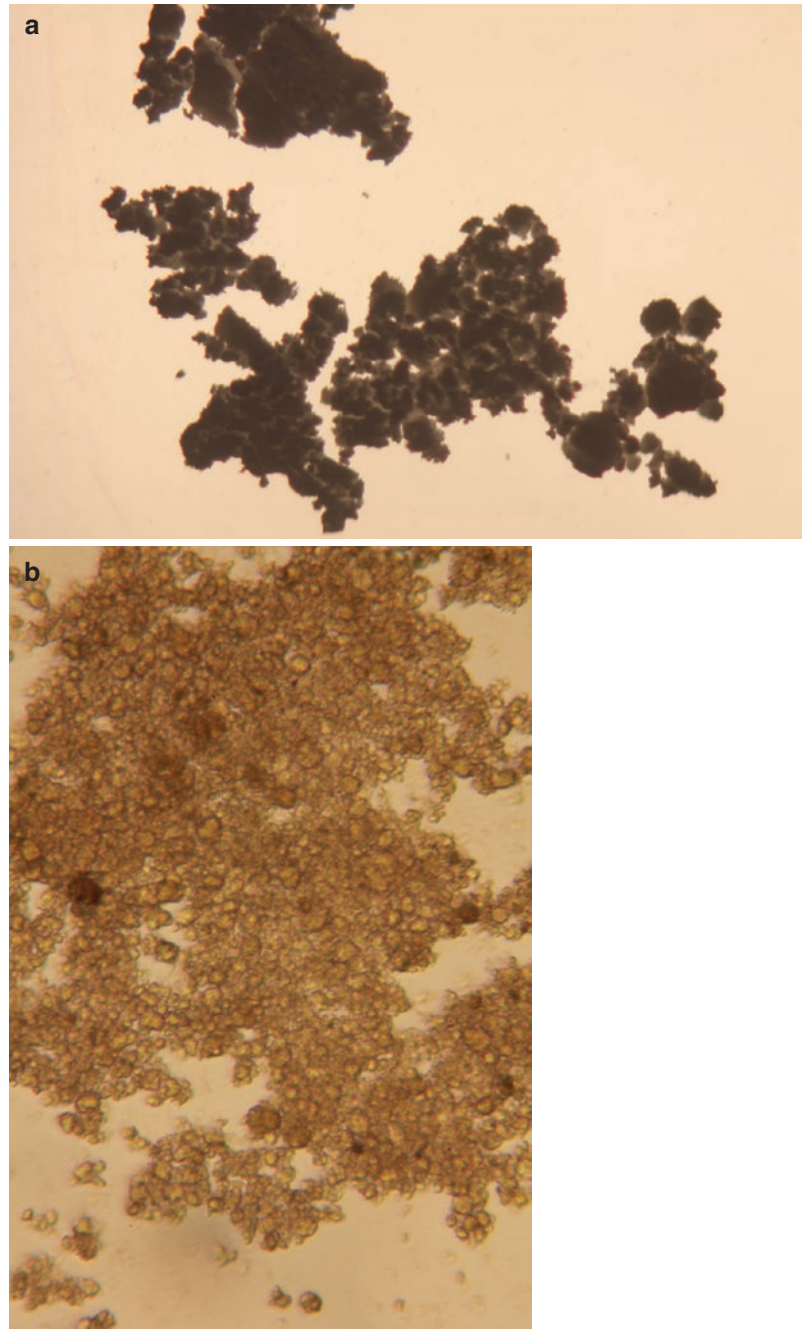

Fig. 34.1 Photographs showing the crystalline structure of titanium dioxide (EOS Rebel T2i; Bresser Microscope MPO 401; magnification, PL4/0.1 160). (**a**) Both large and small particle sizes can be seen. Patch testing with titanium in older studies would have used similar powder with particles sizes up to 100 nm, which will not penetrate the stratum corneum. (**b**) The particle sizes of nanopowders are more uniformly small (about 25 nm) but still too large to penetrate the skin; they can, however, penetrate the oral mucosa [134]

skin was unclear, intracutaneous injections were used to determine and optimize correlations with the results of patch test dose-response series [76]. Perhaps the absence of sufficient patients with a suspected titanium allergy in a single patch testing center of excellence has limited the application of these disciplines in parallel with the great work done on nickel, cobalt, chromium, and gold. Titanium(III) nitride, titanium(IV) carbide, and calcium titanate(IV) are also all water insoluble. We do not have the benefit of skin penetration, guinea pig maximization test (GPMT), or local

lymph node assay (LLNA) studies; yet, these patch test allergens are available commercially, likely simply because they are used as coatings on various implants. A titanium disc fully protected by the spontaneously occurring TiO_2 coating is equally unhelpful in assessing suspected type IV sensitivity. The situation is further complicated by the possibility of alloying metals or trace metals being preferentially released, thereby leading to a false-positive interpretation of a patch test reaction. Wood and Warshaw summarized cases of suspected titanium allergy ultimately found to be caused by another relevant allergen [11]. This scenario is particularly apt to develop when nickel-allergic patients are exposed to the ubiquitous NiTi alloys.

Titanium chloride III and IV have also been used as patch test preparations. Although both are initially water soluble, they decompose to TiO_2. Ikarashi and coworkers evaluated the sensitization of guinea pigs to $TiCl_4$ using the GPMT and LLNA [77]. Of ten guinea pigs undergoing induction of intradermal TiO_2, five were positive on patch test challenge. They also showed mild increases in lymph node weight with $TiCl_4$, but the sensitive LLNA was negative according to the criteria. For patch testing $TiCl_4$ has the added disadvantage of having a low pH, which is likely a contributing factor to reports of irritant reactions (IR) or even false positives. Several doses at log intervals would likely be preferable in order to differentiate between an IR and true contact allergy.

Titanium sulfate is also soluble in water but hydrolyzes to form titanium dioxide. It is not known how quickly hydrolysis occurs on the skin. It is used in the industrial production of rutile TiO_2 and in printing inks. Although commercially available as a catalyst for epoxide synthesis, titanium isopropoxide decomposes rapidly in water or moist air to produce TiO_2. It is unclear how a stable petrolatum preparation can be prepared with this compound.

Titanium(III) oxalate is sparingly soluble in water (insufficient for an adequate patch test dose) and oxidizes in air to TiO_2. Titanium(IV) oxalate is only slightly soluble in water and stable. Its pH, however, is low because of residual oxalic acid content, and a low pH creates concerns about irritant reactions. Recently, a patient was found to be patch test positive to "titanium oxalate" without reference to the exact compound [78]. Reporting patch test results to titanium oxalate without details of oxidation state or the degree of hydration of the patch test substance, which is necessary to determine titanium content and to understand pH, precludes comparisons across studies.

Lalor and colleagues reported negative patch test results using titanium salicylate, titanium tannate, titanium peroxide, and titanium dioxide, four ingredients found in Metanium, an over-the-counter ointment used for decades to treat diaper rash [79]. The specific molecular formulae of these titanium compounds were not reported, making it impossible to replicate their precise use. Suspended, water-insoluble titanium tannate nanoparticles have utility in their ability to adsorb dyes from industrial wastewater due to their porous surface structure and water insolubility—unlikely physicochemical properties for an ideal patch test preparation [80]. Titanium salicylate is an anionic surfactant that is only slightly soluble in water. It is used as a preservative and patented for use in the treatment of rosacea, acne, scars, and skin infections [81, 82]. Its utility as a patch test preparation has not been studied.

Titanium peroxide nanoparticles are of the anatase crystalline structure and able to increase cytotoxic effects of x-ray irradiation against pancreatic cancer because of the increased production of reactive oxygen species [83]. The suspended Ti peroxide nanoparticles also adsorb dyes similar to titanium tannate [84]. Not surprisingly, these three titanium compounds produced negative patch test results in all five patients tested by Lalor et al. [79]. Unexpectedly, two positive reactions were observed when patch testing with the combination in the Metanium ointment. These two positive patch test reactions, however, could have been the result of other ingredients in the formulation known to be contact allergens, including tincture of benzoin [85].

Calcium titanate is a synonym of calcium titanium oxide, another water-insoluble nanoparticle used for the immobilization of radioactive waste and as a fire retardant. Application to the surface of an implant as a bioactive coating has likely led to its use as a patch test allergen [86].

The efficacy of an in vivo titanium allergy test depends on antigen penetration through the stratum corneum. Such penetration is unlikely in sufficient concentration with TiO_2, titanium nitride, titanium tannate, titanium carbide, calcium titanate, or titanium propoxide nanoparticles. Some investigators have had success with prick testing with TiO_2 although they interpret the positive reactions as Type 1 sensitization [87]. If convincing data emerge that TiO_2 nanoparticles do indeed function as relevant type IV antigens, pretreatment of the skin with microneedle patches or intracutaneous injection may be worth exploring to overcome the penetration obstacle [88].

A stable, solvent-soluble, protein-reactive titanium salt that penetrates the skin is needed for patch testing. The water-soluble metal salt approach has been successful with other metals; consequently, ligands that render Ti(IV) stable in solution need to be explored. Stable, water-soluble candidates include titanium ascorbate, sodium titanium dimalate, titanium digluconate, sodium titanium citrate, ammonium titanium glycolate, ammonium titanium(IV) oxide oxalate, ammonium titanium(IV) peroxo citrate, titanium(IV) lactate ammonium hydroxide, and titanium(IV) lactate tetramethylammonium hydroxide [89–92]. Additional candidates soluble in ethanol are titanium octanoate, octylene glycol titanate, and tetrakisethylsiloxy titanate or titanium decanoate miscible in cyclomethicone [89].

Ammonium titanium lactate, sodium titanium citrate, ammonium titanium glycolate, titanium octanoate, octylene glycol titanate, tetrakisethylsiloxy titanate, and titanium decanoate are known to induce superficial blockage of pores. This property led to their consideration as alternatives to aluminum chlorohydrate for use in antiperspirants [89]. Despite the tendency of these multivalent metals to form polymeric gels able to block pores, some ion penetration occurs and is measurable in serum following axillary absorption from an antiperspirant preparation. This finding contributed to concern about aluminum carcinogenicity and estrogen action [93].

In another study, subjects participating in a trial evaluating a novel antiperspirant based on ammonium titanium lactate developed axillary rashes. Twelve of these subjects were patch tested with ammonium titanium lactate and also with 10% titanium dioxide and other common metal allergens. Their findings were compared to other participants who had not developed the skin rash as well as to a group who had never knowingly been exposed to ammonium titanium lactate. In each group there were a few positive reactions to a common metal allergen, but none of the naïve subjects and none of the subjects who had not developed a reaction during the original trial had a positive reaction to either the titanium dioxide or titanium lactate. Of the 12 patients who had had a reaction during the trial, 3 had a positive reaction to the titanium lactate but not to the titanium dioxide. The specific molecular formula with degree of hydration was not reported [94].

Currently, the diagnostic efficacy of a series of metals is being evaluated for patch testing in the T.R.U.E. TEST hydrogels. Five different stable, water-soluble titanium salts in three different concentrations each (Table 34.4), including an ammonium titanium lactate (titanium(IV) lactate ammonium hydroxide), are among the com-

Table 34.4 Titanium salts under investigation by SmartPractice

Titanium salt	Concentration (mg Ti/cm^2)
Titanium citrate	
Ammonium titanium peroxo citrate	0.055
	0.11
	0.22
Titanium lactate	
Titanium(IV) lactate ammonium hydroxide	0.070
	0.14
	0.28
Titanium(IV) lactate tetramethylammonium hydroxide	0.32
	0.16
	0.080
	0.040
Titanium oxide oxalate	
Potassium titanium oxide oxalate	0.060
	0.12
	0.24
Ammonium titanium oxide oxalate	0.055
	0.11
	0.22

pounds being tested. At the time of this writing, quantitative analytical methods have been developed, stability of the patches has been established, and blinded prospective clinical trials are underway (Fig. 34.2). While it is hoped that this trial will identify the most effective hydrogel and petrolatum formulations for titanium patch testing, complying with all regulatory requirements means that it will still be years before a licensed product might become available. In the interim in the United States, availability from a compounding pharmacy allergen bank on a patient-specific prescription basis is an alternative.

34.4.2 Timing of Patch Testing: Before or After Implants?

Opinions vary about the need for patch testing in candidates for medical or dental implants. When patch testing is to be conducted, its timing—before or after placement of the implant—has also been questioned. Although general guidelines for patch testing for metal allergies in this situation have been proposed [71], it must be remembered that the timing of patch testing is irrelevant unless it is conducted with an efficacious substance. Consequently, even though Honari and coworkers,

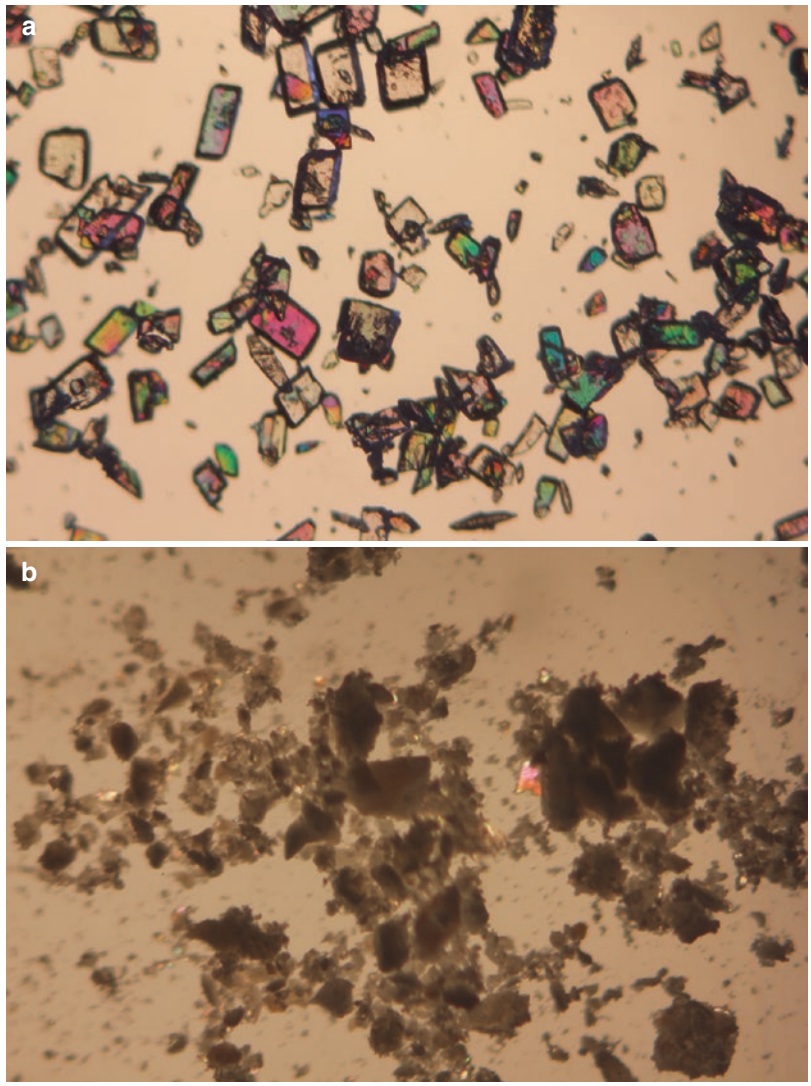

Fig. 34.2 Photographs showing the crystalline structure of (**a**) potassium titanium oxide oxalate dihydrate and (**b**) titanium(III) oxalate (EOS Rebel T2i;

for example, suggested patch testing with titanium dioxide and titanium powder as part of a broad series of metal allergens in conjunction with a baseline series prior to patients receiving an endovascular implant [95], these substances, as discussed, are unlikely to be effective diagnostics.

34.4.3 In Vitro Tests

In vitro tests such as leucocyte transformation, migration inhibition, and cytokine production have also been explored as diagnostic alternatives for determining titanium sensitization. Lymphocytes from the peripheral blood of suspected allergic patients and controls are incubated with titanium, and evidence of sensitization is measured. The methods with and without radioactive hydrogen labeling used to assess leucocyte proliferation, the modified and Boyden chamber technique to measure leucocyte migratory capacity, and the enzyme-linked immunosorbent assays for specific cytokines are described elsewhere [96–100].

The lack of standardized, validated, and regulated methods and the difficulty transporting viable patient-specific monocytes in sufficient quantity to reproducibly perform the tests make comparisons of results across laboratories and studies difficult. The selection of the titanium compound used to incubate with the lymphocytes may be one of the significant variables contributing to some of the differences across laboratories and between published studies. Most laboratories have used insoluble TiO_2 of various nanoparticle sizes and with different or unknown ratios of rutile and anatase forms. When these same in vitro tests have been performed with other metals, soluble salts have been used.

Pellowe and coworkers appear to have developed an ionic titanium antigen by complexing titanium with human serum albumin (HSA), which was subsequently used for LTT and cytokine profiling [101]. The investigators incubated titanium citrate with HSA to produce stable ionic Ti antigens. When peripheral blood mononuclear cells were evaluated, proliferation was elevated in the serum of all six patients tested. Expression of interleukin (IL)-12 and tumor necrosis factor (TNF)-α increased in the Ti implant patients compared to the patients without implants when incubated with the ionic Ti antigen, while IL-10 decreased in implant patients when incubated with TiO_2 nanoparticles [101]. Hallab et al. showed similar results following the incubation of Ti-6Al-4V beads in human serum [102]. The concentrations of Ti in the serum fraction correlated with the LTT response. They found two molecular weight ranges of serum proteins (<30 kDa and 180–250 kDa) binding the Ti. The higher molecular weight fraction showed higher LTT reactivity. It is not known if the protein binding is with Ti ions or with TiO_2 forming spontaneously following release from the metallic beads.

Vamanu and colleagues had previously described a method to form stable HSA-TiO_2 antigens in physiologic solutions, which they proposed for use with LTT [69]. Their transmission electron microscopic images of TiO_2 aggregates and their decreasing number in the presence of HSA were interpreted as supporting evidence of the dose-dependent concentration of TiO_2 in suspension due to antigen formation. Their use of inductively coupled plasma mass spectrometry accurately measures the concentration of Ti in the physiologic solutions but does not differentiate Ti content between Ti ions and TiO_2. It is unclear why more work has not been done exploring the use of stable water-soluble titanium salts rather than insoluble TiO_2 for in vitro test research.

In general, the low specificity and sensitivity of the LTT for metals other than nickel have limited its adoption as a clinical tool. Positive LTTs in patients suspected of implant hypersensitivity due to titanium have ranged from 0% to 42%. Recently, Wood and Warshaw summarized the LTT for titanium hypersensitivity in clinical series [11]. In an effort to improve diagnostic sensitivity, Hallab et al. suggested using the results of LTT, lymphocyte migration inhibition, and specific cytokine production in conjunction with each other [103]. Using this approach Vermes and coworkers prospectively followed controls and implant patients for 36 months [104]. They found that titanium reactivity increased significantly after the placement of well-functioning titanium implants.

These evolving in vitro approaches with increased standardization and regulatory oversight will be meaningful for the further elucidation of immune mechanisms catalyzed by Ti exposure but are unlikely to offer a pragmatic logistical and economically viable diagnostic solution any time soon. Not surprisingly, the results of nonstandardized in vitro tests correlate poorly with the results of nonstandardized titanium patch tests.

34.5 Clinical Implications

Currently, the *reported* prevalence of contact allergy to titanium is low. Some researchers, however, have suggested that it may be grossly underreported, especially in terms of dental implant titanium hypersensitivity [87, 105]. A recent Delphi consensus study of expert orthopedic surgeons responding to questions about metal allergy suggests a similar situation. The majority agreed that patients undergoing metal arthroplasty surgery need not be routinely questioned about metal allergy before surgery. The predictive value of Delphi studies can be high, but based on the participants' reported comments, awareness of metal-related allergies, let alone those related to titanium, would appear to be limited [106]. If the finding is generalizable to the orthopedic community at large, most reactions related to titanium implants likely go unrecognized even while the frequency of implant surgeries continues to rise. It is also worth noting that patients are now being reported whose choice of implant is being dictated by their personal claims of preoperative positive patch test reactions to titanium. In one such case a patient with severe symptomatic sick sinus syndrome received a gold-coated pacemaker apparently on the basis of a self-report of a "proven type IV allergy to titanium" determined by patch testing months before his cardiac condition became symptomatic [107].

Statistics related to the frequency of implant procedures further support the contention that titanium-related reactions may be underreported. Based on a 2013 study from the Organization for Economic Cooperation and Development (OECD), which includes 34 member countries, Switzerland, Germany, and Austria performed the most hip replacements (292, 283, and 276 per 100,000 population, respectively), while the United States performed the most knee replacement surgeries followed by Austria (226 and 215 per 100,000 population, respectively) [108]. The same study reported that the average rate of hip replacement procedures across the OECD members increased about 35% between 2000 and 2013 while that of knee replacements doubled. Other researchers applied 2010 prevalence data to 2030 population estimates and predicted that in the United States alone, 11 million individuals will undergo a total knee or hip replacement in 2030 [109]. The rate of dental implants is also expected to continue increasing. In 2013 in the United States, 1,260,000 dental implants procedures were performed, a figure predicted to double in just 7 years [110]. Whether the number of reports of clinical allergy related to these burgeoning numbers of procedures will also increase remains to be seen, but it would not be surprising based on their volume alone.

To date more than 30 different signs and symptoms have been associated with exposure to titanium, most, but not all, related to medical or dental implants (Table 34.5). Dermatitis, pruritus, and pain have been the most common. Based on a search of the FDA's Medical Device Adverse Event Database (MAUDE) using the keywords, "titanium allergy," 49 cases of adverse events related to titanium medical devices were reported by consumers between 2001 and 2016 (Table 34.6) [111]. Numerous cases of patients with medical or dental titanium implants needing revision surgery have also been reported (Table 34.7, Figs. 34.3 and 34.4). European data indicate that the number of implant revision procedures is increasing. In Sweden alone, for example, the rate of revision of surgery for total hip replacements due to aseptic loosening, adverse soft tissue reactions, and pain—all of which have been reported to be associated with cases with titanium implants thought to be associated with titanium hypersensitivity—is more than 50% (Table 34.8). In some implant cases, multiple revision procedures have been performed; in some cases, implants have been replaced with devices made from other materials; and in some cases, devices have simply

Table 34.5 Summary of clinical presentations in cases associated with exposure to titanium[a]

Clinical presentation	No. of cases	Reference
Dermatitis/eczema/rash	14	Brun and Hunziker [137], Viraben et al. [138], Ishii et al. [131], Yamauchi et al. [139], Thomas et al. [114], Müller and Valentine [140], Egusa et al. [116], Sicilia et al. [87], van Opstal and Verheyden [125], Kikko et al. [141], Ko et al. [119], Olsen et al. [78], Hosoki et al. [123]
Erythema (redness)	8	Peters et al. [129], du Preez et al. [115], Sicilia et al. [87], Oliva et al. [142], Goto et al. [117], Kikko et al. [141]
Exacerbation of atopic dermatitis	1	Tamai et al. [112]
Exanthema	1	Belohlavek et al. [130]
Swelling	7	Peters et al. [129], du Preez et al. [115], Sicilia et al. [87], van Opstal and Verheyden [125]
Pruritus (itching)	11	Peters et al. [129], Egusa et al. [116], Sicilia et al. [87], Oliva et al. [142], Goto et al. [117], Belohlavek et al. [130], Kikko et al. [141]
Aseptic purulent drainage	1	Verbov [127]
Generalized nummular dermatitis	2	Buchet et al. [128], Yamauchi et al. [139]
Skin vesicles and erosion	1	Abdallah et al. [124]
Serous fluid collections	1	Abdallah et al. [124]
Conjunctivitis	1	Tiesenga et al. [143]
Granulomatous (foreign body) reaction (including nodular, pyogenic, and peripheral giant cell)	6	Viraben et al. [138], Ishii et al. [131], du Preez et al. [115], High et al. [144], Olmedo et al. [145]
Device exposed	1	Ishii et al. [131]
Device loosened	1	van Opstal and Verheyden [125]
Wound necrosis	1	Syburra et al. [122]
Pain/burning	13	Langford and Frame [146], Mylanus et al. [113], du Preez et al. [115], van Opstal and Verheyden [125], Tiesenga et al. [143]
Hyperemia of soft tissue	1	du Preez et al. [115]
Persistent gingival hyperplasia	2	Mitchell et al. [118]
Peri-implant mucositis (gingivitis)	2	Egusa et al. [116], Lim et al. [24][b]
Mobility of dental implant	3	Takarada and Kinebuchi [147], Sicilia et al. [87]
Spontaneous rapid implant exfoliation	4	Deas et al. [148], Sicilia et al. [87]
Oral lichen planus	1	Takarada and Kinebuchi [147]
Allergic contact stomatitis	1	Lim et al. [24]
Glottal edema	1	Sicilia et al. [87]
Chronic inflammatory response	1	du Preez et al. [115]
Sinusitis	1	Tisenga et al. [143]
Impaired fracture healing	1	Thomas et al. [114]
DRESS syndrome[c]	1	Nawaz and Wall, [149]
Inflammatory arthritis	1	Dörner et al. [150]
Death	2	Hettige and Norris [151], Brahimaj et al. [152]
Granulomatous pulmonary disease	1	Redline et al. [153]
Fever	3	Sakamoto et al. [126], Wang et al. [121]
Eosinophilia	2	Sakamoto et al. [126]
Pleural effusion	2	Sakamoto et al. [126]
Yellow nail syndrome	16	Berglund and Carlmark [154]

[a]Includes medical and dental implants as well as occupational and consumer exposures
[b]Reacted to TiN-coated implant abutment; improved when replaced with CpTi abutment
[c]*DRESS* drug rash with eosinophilia and systemic symptoms

Table 34.6 Types of titanium devices related to complaints reported to the US Food and Drug Administration between 2001 and 2016

Type of device	No. of complaints ($n = 49$)
Cardioverter	6
Dental	5
IUD	3
Femoral rod	1
Hip	3
Infusion pump	9
Lumbar graft	1
Neuromodulator	14
Pacemaker	3
Pulse generator	1
Spinal rod	1
Tibial plate	1
Vascular closure	1

been removed when feasible, often with improvement or resolution of symptoms (Table 34.7) [78, 112–131]. Most of these cases have been reviewed by Wood and Warshaw and by Fage and coworkers [11, 62]. Although titanium allergy is rare and may continue to be so overall, it is difficult to avoid concluding that cases of titanium allergy are likely to increase.

Even while the evidence in support of titanium as a metal allergen mounts, the existing literature must be interpreted with caution. As discussed, the clear lack of a reliable titanium formulation for patch testing casts doubt on negative patch test reactions, especially in symptomatic patients with titanium implants or in those whose symptoms have improved after implant removal. Although

Table 34.7 Cases whose symptoms improved or resolved after removal of titanium implants or devices (with or without adjuvant treatment)

Type of implant	No. of patients	Reference
Dental		
Mandibular ($n = 6$)	1	du Preez et al. [115]
Abutments	2	Mitchell et al. [118]
Mandibular support for overdenture ($n = 2$)	1	Egusa et al. [116]
Intraoral restorations ($n = 17$)	1	Ko et al. [119]
TiN implant abutment	1 (successfully replaced with CpTi abutment)	Lim et al. [24]
Dental implants	1 (orthopedic screws improved eczema followed by resolution after removal of dental implants	Hosoki et al. [123]
Medical		
Pacemaker	1	Buchet et al. [128], Ishii et al. [131], Freeman [155], Syburra et al. [122], Shittu et al. [120]
	1 (successfully reimplanted coated device)	
	1 (replaced with gold device)	
	1 (replaced with gold device)	
	1 (multiple unspecified exchanges of components in patient with a positive patch test to Ti; symptoms resolved when replaced with gold device)	
Nitinol foramen ovale occluder	1	Belohlavek et al. [130]
Plates/screws	1 (for metacarpal fracture)	Thomas et al. [114], Kikko et al. [141], van Opstal and Verheyden [125], Wang et al. [121]
	1 (for leg injury)	
	1 (tibial baseplate)	
	2 (screws for hallux valgus)	
Craniofacial implants (bone-anchored hearing aid)	7 implanted, pain improved in 6 after removal	Mylanus et al. [113]
Suture anchors	1 (for rotator cuff)	Goto et al. [117]
Surgical clips	1 (for cholecystectomy)	Tiesenga, et al. [143]
Nuss procedure bars	1	Sakamoto et al. [126]
Spinal cage	1 (successfully replaced with polyetherketone cage)	Dörner et al. [150]
Lower leg hardware	1 (for ankle fracture)	Olsen et al. [78]

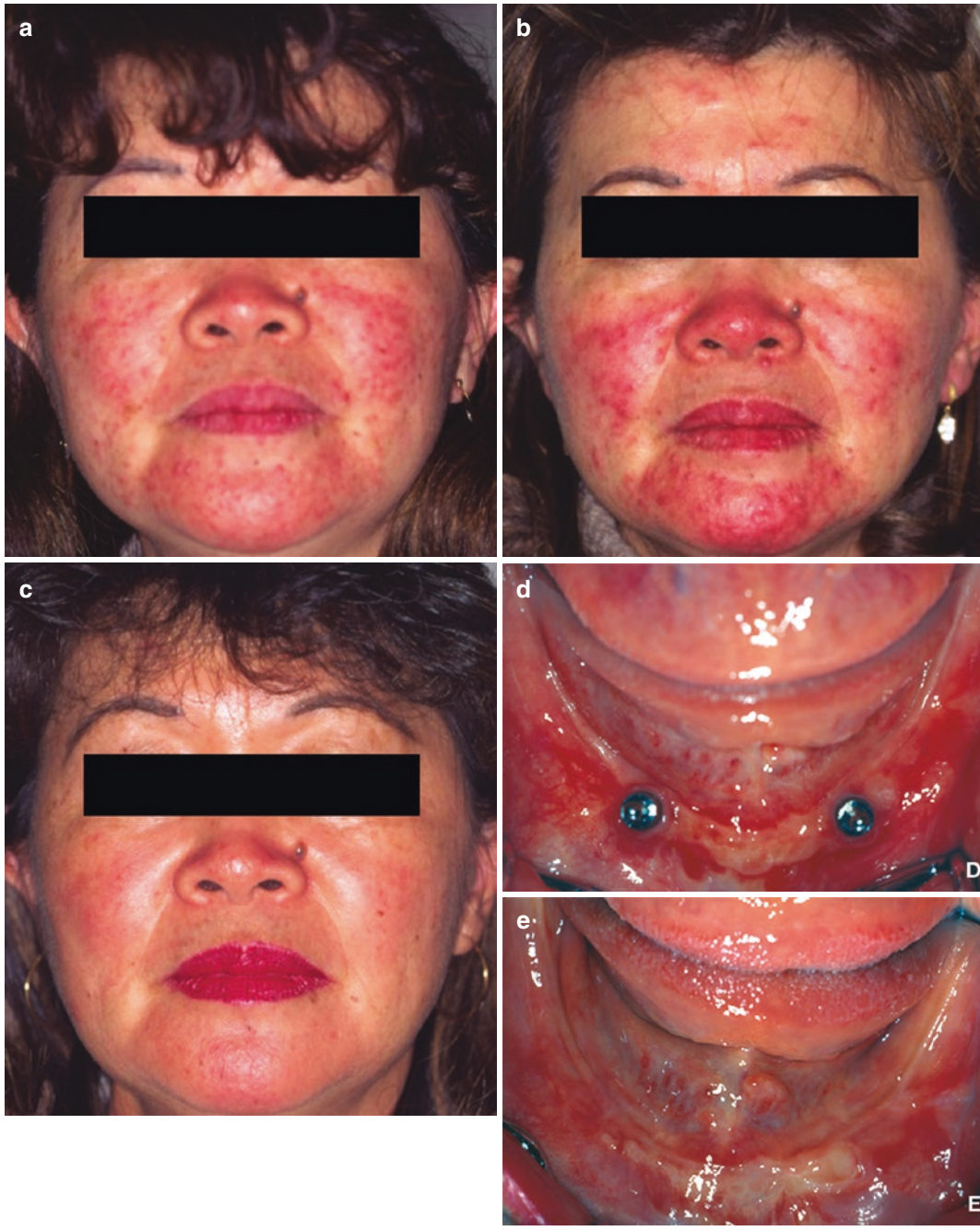

Fig. 34.3 (**a**) Photograph of a patient who developed facial eczema that had persisted for 2 years after she received titanium dental implants. (**b**) One week after her implants were removed, her symptoms worsened, which was attributed to the rechallenge represented by titanium debris resulting from the procedure. (**c**) However, 10 months after removal of the implants, the patient's symptoms had resolved. Appearance of the maxillary arch (**d**) with implants and (**e**) 10 months after their removal. (Reproduced with permission from [116])

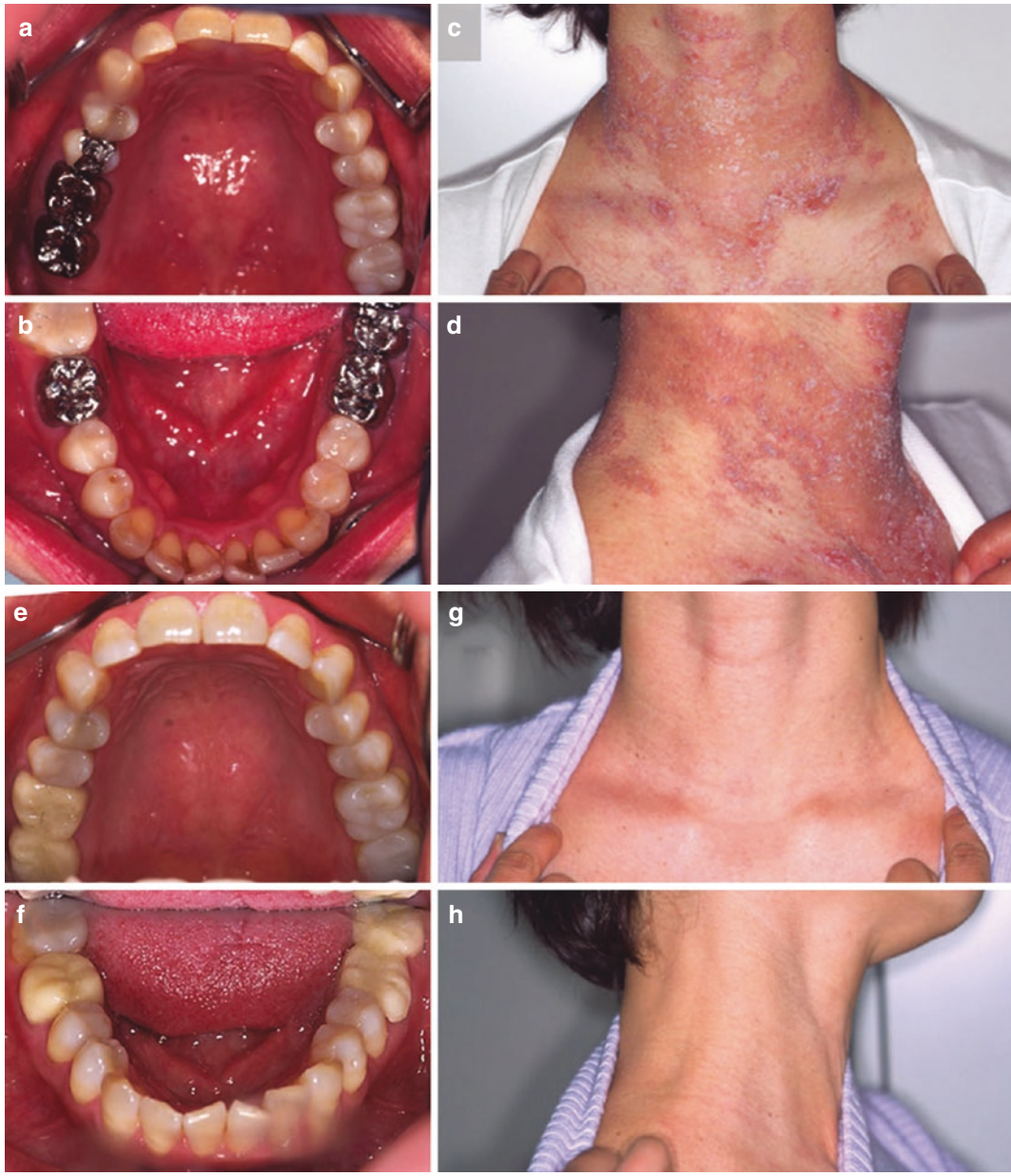

Fig. 34.4 Intraoral views of the (**a**) maxillary and (**b**) mandibular arches of a woman with titanium crowns. Nine months after the prosthetic treatment, she developed worsening eczema on her neck, seen in (**c**) frontal and (**d**) lateral views. The implants (**e**, maxillary, and **f**, mandibular views) were removed, and within 3 months the patient's eczema resolved (**g**, frontal, and **h**, lateral views). (Reproduced with permission from [119])

improvement in symptoms after removal of a titanium implant does not prove the existence of a titanium allergy, the association is certainly noteworthy. The identity of implants and their component alloys are not always reported; often, the information may be unavailable. When available, however, as much identifying information as possible should be included in publications because

Table 34.8 Characteristics[a] of first recorded revision of total hip replacement procedures conducted in Sweden and parts of the United Kingdom from 1979 to 2014

Reason for revision	1979–2009	2010	2011	2012	2013	2014	2015	Total	%
Sweden[b]									
Aseptic loosening	22,232	1068	989	977	918	853	NR	27,037	52
Others	1,013	32	37	51	92	59	NR	1,284	3
Pain only	386	19	18	29	21	46	NR	519	1
Total	39,816	2402	2330	2357	2345	2365	NR	51,617	56
England, Wales, Northern Ireland, Isle of Man[c]									
Aseptic loosening	3654	3700	3776	3881	3659	35,324	38,310	56,980	46
Pain	2032	2000	2114	2219	3489	16,358	16,875	28,729	23
Adverse soft tissue reactions	86	410	982	1286	NR	5201[d]	6149[e]	2764	3[f]
Total	6610	7375	8201	8812	14,903	70,696	78,130	124,031	69

NR not reported
[a]Characteristics are not mutually exclusive
[b]The Swedish Hip Arthroplasty Register Annual Report 2014
[c]National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man 10th–13th Annual Reports
[d]*n* = 51,741 adverse reactions to particulate debris
[e]*n* = 54,804 adverse reactions to particulate debris
[f]*n* = 109,128

hypersensitivity can also be mistakenly attributed to titanium. This situation is highlighted by the case of a patient in need of an orthopedic implant who was suspected of having a titanium allergy because she had developed a facial contact allergy related to her "titanium" glass frames. She had positive patch test reactions to nickel, cobalt, and palladium, all of which were identified in her frames, which included only a trace amount of titanium [132]. The number of metals that can be present in titanium alloys makes it mandatory to rule out other potential allergens as the underlying cause of a patient's type IV hypersensitivity [133].

The paucity of reliable data concerning almost every aspect of titanium hypersensitivity offers many conundrums whose resolution will await more carefully conducted research and increased clinical awareness. Answers, however, will not be forthcoming if clinicians continue to patch test with allergen preparations, including TiN, TiO_2, Ti tannate, Ti carbide, Ti peroxide, Ti isopropoxide, calcium titanate, discs, and powders, whose known physicochemical characteristics contribute to false-negative reactions.

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Metal Allergy: Other Metals

35

Andreas J. Bircher

35.1 Introduction

Apart from the frequently sensitizing metals nickel, cobalt, chromium, palladium, and others such as gold and copper, many more metals exist which have been more rarely reported to elicit contact allergy [1]. Some of these commonly occurring metals such as titanium and aluminum present in medical implants and devices [2] are discussed in other chapters in this book. Here, we focus on other metals, some of which are essential trace elements that have been very rarely reported to be contact sensitizers, even though the human organism may be exposed to them occupationally or via the use of topical and systemic drugs, oral intake in food, or implantation of medical devices such as orthopedic implants, pacemakers, stents, and dental materials. From a theoretical point of view, some of these metals such as antimony, cadmium, iron, molybdenum, niobium, lead, silver, titanium, vanadium, zinc, and zirconium do not form metal ions and appear to have therefore little to no sensitizing capacity [3].

One of the main issues is the lack of standardization of testing regarding these potential metal contact allergens. Although there are case reports and studies on metal series which have been tested in selected populations such as in patients with dental problems or complications from orthopedic implants, there is little information on the optimal test conditions such as the most suitable metal salts, the test concentrations, or the vehicles to be used. The test conditions for the following respective metals have been identified by us in the literature or are commercially available. Even if positive patch test results to rare metals have been reported, this information should be used with caution. Often there is no sufficient standardization and validation; therefore, the results of such reports should be applied and interpreted with caution. In addition, many metal compounds may be irritants, as it was recently demonstrated, e.g., for manganese [4]. The inherent toxicity or irritant potential of some metals renders the reading and interpretation of test results and the performance of prospective studies difficult.

35.2 Selected Metals

35.2.1 Antimony

35.2.1.1 Properties and Occurrence

Antimony belongs to the group of half-metals. Metallic antimony is silvery and is used in fireproof clothes as well as for hardening lead-containing alloys. Previously, it was used in the rubber and ceramic industry [5].

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35.2.1.2 Test Conditions

- Antimony metal [6]
- Antimony potassium tartrate 3% aqueous solution (aq.) [7]
- Antimony tartrate 2%, unknown vehicle [6]
- Antimony trichloride 1% petrolatum (pet.) [8]
- Antimony trioxide powder [7, 9]
- Antimony trisulfide 2% aq. [7]

35.2.1.3 Clinical Observations

A worker with occupational exposure to antimony trioxide in the production of fireproof wrappings developed a generalized lichenoid contact dermatitis. Patch tests with antimony trioxide (concentration and vehicle unknown) were positive [6]. In a series of workers in the ceramic industry, two had a positive patch test to antimony trioxide [9]. Antimony has an irritant potential and may induce an irritant folliculitis [5].

35.2.2 Arsenic

35.2.2.1 Properties and Occurrence

Arsenic is a highly toxic metal existing in an organic as well as inorganic form, with metallic as well as nonmetallic properties [6]. It was used in the past in medicine and dentistry and is still used in some herbicides, in the glass and crystal industry, and as pigment [6]. Arsenic is a lethal poison, and chronic exposure to inorganic arsenic compounds may result in skin carcinomas; in the past, *Liquor Fowleri* (potassium arsenate) was used in the treatment of psoriasis.

35.2.2.2 Test Conditions

- Arsenic 1% pet. [7]
- Arsenic trioxide powder [5, 6]
- Potassium arsenate 1% aq. [7]
- Potassium arsenite pure [7]
- Sodium arsenate 10% aq. [10]
- Sodium arsenate 1% aq. [11]

35.2.2.3 Clinical Observations

In 71 workers of a copper-melting plant, sensitization to arsenic was documented and resulted in eczematous, pustular, and follicular lesions. The distribution showed a pattern of airborne exposure [11].

A glassblower with hand dermatitis as well as lichenoid dermatitis on air-exposed areas had a positive patch test to arsenic trioxide powder [5].

In a series of 379 patients with dermatitis, patch tests with sodium arsenate and sodium arsenite (concentrations and vehicles unknown) were performed. Two patients had positive reactions; the relevance was, however, not clear [12]. Arsenic can also elicit irritant contact dermatitis as observed in 11 workers of a tin-smelting factory; patch tests were not performed [13]. Analysis of eye shadows showed a very low content of arsenic not indicating a health hazard [14].

35.2.3 Cadmium

35.2.3.1 Properties and Occurrence

Cadmium is used as a corrosion inhibitor and coloring agent, as well as dental prostheses. In addition, it is used as stabilizer in plastics, in dry batteries, and in photochemistry [15]. It is sometimes found in jewelry, paint, and makeup, although it may be hazardous for the human organism [16, 17].

35.2.3.2 Test Conditions

- Cadmium chloride 0.1%, 0.5%, and 1% pet. [15]
- Cadmium chloride 2% pet.
- Cadmium sulfate 2% pet.

35.2.3.3 Clinical Observations

In a series of 662 patients the German Contact Dermatitis Research Group tested cadmium chloride in 3 concentrations in pet. With the 1% concentration, 6.9% positive tests were observed, all of them without relevance, but also with many questionable and irritant reactions. A test concentration of 0.5% was recommended, which should only be used in patients with suspected exposure from cadmium [15].

35.2.4 Gallium

35.2.4.1 Properties and Occurrence

Gallium is a silvery-white metal with properties similar to aluminum. It is used in dental alloys and in scintigraphy (gallium 67).

35.2.4.2 Test Conditions

- Gallium chloride 10% pet. [18]
- Gallium oxide (unknown concentration and vehicle)

35.2.4.3 Clinical Observations

In a series of 63 patients with dental restorations, no positive test reactions to gallium 10% pet. were observed. In a female patient, a positive test reaction to gallium oxide without the establishment of relevance was found [19]. A 38-year-old mine worker with suspicion of silicosis suffered from severe long-lasting urticaria and joint pain requiring prednisone, after having received gallium 67 for scintigraphy. A prick test with the preservative benzyl alcohol was positive, and a patch test with several components negative. Due to its radioactivity, gallium 67 could not be used for testing; other gallium compounds were not tested. Immune complexes were elevated, indicating an immune-complex reaction due to benzyl alcohol [20].

35.2.5 Indium

35.2.5.1 Properties and Occurrence

Indium is a rare, soft heavy metal that is used in the production of flat-screens and touch screens. In dental medicine, it is an additive used in some alloys as a catalyst and in order to increase their hardness.

35.2.5.2 Test Conditions

- Indium 1% pet.
- Indium(III) chloride 1%, 5% and 10% aq. [7, 18, 21, 22]
- Indium sulfate 3.16% and 10% aq. [5, 22]

35.2.5.3 Clinical Observations

In a dental screening series, 205 patients were tested with indium and iridium; in 7, positive reactions to indium chloride have been reported [23]. Among over 300 patients tested with a metal series, we have observed only two cases of a strong positive reaction to indium. Interestingly, both were positive to indium chloride but not to indium sulfate and indium metal 1% pet. All had positive reactions to other metals such as nickel, palladium, rhodium, and gold, raising the issue of cross-reactivity or potential contaminations.

35.2.6 Iridium

35.2.6.1 Properties and Occurrence

Iridium is a very rare metal that belongs to the group of transition metals of the platinum group. It is very hard and brittle [24]. It is used in the electrochemical industry, as the cathode in x-ray sources, and is found in trace amounts in gold- and mercury-containing dental alloys.

35.2.6.2 Test Conditions

- Ammonium hexachloroiridate 0.032%, 0.1%, and 1% aq. [5, 22]
- Iridium 1% pet.
- Iridium(III) chloride 1% aq. [22, 24]
- Iridium(IV) chloride 1% aq. [8]

35.2.6.3 Clinical Observations

In a dental series of 205 patients [23], iridium chloride resulted in 4 positive test reactions without the establishment of clinical relevance. An occupationally exposed worker reacted with contact urticaria and respiratory symptoms to iridium chloride. A positive prick test to iridium chloride was observed; a scratch test resulted in an anaphylactic reaction [25]. Among over 300 patients patch tested with a metal series, we have observed five cases of very strong positive test reactions to iridium, some with long persistence and granulomatous character. Interestingly, all were also positive to nickel and palladium, some

also to other metals such as cobalt, and one patient was also positive to indium. A few also had irritant reactions to vanadium and manganese. As with indium, the concomitant reactions to several metals raise the issue of co-sensitization, cross-reactivity, or potential contaminants in test substances.

35.2.7 Iron

35.2.7.1 Properties and Occurrence

Iron is a heavy metal and an important essential trace element for the human organism. Naturally, it occurs as black iron oxide (magnetite), red iron oxide (hematite), and yellow-brown hydrated iron oxide (limonite). It is widely used in industry in different steel alloys. Contact allergy from iron seems to be exceedingly rare. In recent years, hypersensitivity reactions from intravenous iron products have been reported more often. However, in this situation, more likely the carbohydrate shell and not the iron hapten appears to be the culprit [26].

35.2.7.2 Test Conditions

- Different iron salts such as iron(III) chloride and yellow and red iron oxide have been mainly tested in 2% concentrations in either petrolatum (pet.) or aqueous solution (aq.) [5, 7–9, 12, 22, 27–29].
- Iron sulfate 5% and 10% aq. [5, 7].
- Iron citrate 5% aq. [12, 18].

35.2.7.3 Clinical Observations

Very rarely, contact allergy from iron has been reported upon occupational exposure [6, 30, 31]. Two patients were occupationally exposed and had a contact sensitization to ferric chloride only, without contact hypersensitivity to other metals. Hemmer et al. [32] identified two patients with positive skin tests to ferric chloride and ferric sulfate; both had also positive skin tests to other metals, such as nickel and cobalt. Van Loon et al. [18] reported two patients from a series of patients tested for contact hypersensitivity to dental materials who had positive skin tests to ferric chloride. Two female patients with positive tests to iron oxides and contact dermatitis from mascara [33, 34] have also been reported. In a study on orthopedic patients with total hip replacement, positive allergic tests to iron chloride 2% were present in a small number, which were, however, considered to be clinically irrelevant [35].

35.2.8 Lead

35.2.8.1 Properties and Occurrence

Lead is a very heavy and soft gray metal. It has been used previously in water pipes and tin cans and has been a component of gasoline and dyes. Lead compounds may result in neurological and hematological toxicity. It may also be present in cosmetics [14], although this is not legal [16, 17].

35.2.8.2 Test Conditions

- Lead acetate 0.5% aq. [5, 6]
- Lead arsenate 20% pet. [7]
- Lead(II) chloride 0.2% aq. [6]
- Lead monoxide 2% in alcohol [7]

35.2.8.3 Clinical Observations

Allergic contact reactions from lead are extremely rare: a truck driver who had dermatitis after contact with accumulators showed positive patch tests to lead chloride 0.2% aq. and lead acetate 0.5% aq. [6].

35.2.9 Magnesium

35.2.9.1 Properties and Occurrence

Magnesium is a silvery, shiny light metal. It belongs to the essential trace elements and is mainly used in alloys. It has been also used as an experimental anti-inflammatory agent in eczema [36].

35.2.9.2 Test Conditions

- Magnesium carbonate (pure) [7]
- Magnesium chloride 5% pet. [22]
- Magnesium myristate 10% pet. [7]
- Magnesium oxide pure [7]
- Magnesium peroxide 10% pet. [7]
- Magnesium stearate pure [7]
- Magnesium sulfate 1% aq. [7]

35.2.9.3 Clinical Observations

So far, no cases of contact allergy to magnesium have been described in the literature. In a study on guinea pigs, no sensitization could be demonstrated [37].

35.2.10 Manganese

35.2.10.1 Properties and Occurrence

Manganese shows a similar chemical reactivity as iron; however, it oxidizes less rapidly. It is often used in alloys with iron and other metals [38, 39], and it is also an essential trace element in several enzyme systems, e.g., in manganese superoxide dismutase.

35.2.10.2 Test Conditions

- Manganese chloride 2% and 5% pet. [7, 8, 22]
- Manganese dioxide 10% pet. [7, 9]
- Manganese(IV) oxide 2.5% and 10% pet. [4, 40]
- Potassium manganese(VII) oxide ($KMnO_4$) 2.5% pet. [4]

35.2.10.3 Clinical Observations

A few cases of contact allergy to manganese have been reported. Previously, the test concentration used was manganese chloride 5% in petrolatum [41–43]. In a patient with an extensive exanthema after the insertion of an osteosynthesis steel plate containing 2% manganese, a positive reaction to manganese chloride 2% and gold was found. After removal of the plate, the exanthema cleared [44].

In our earlier experience with a large series of patients, manganese chloride 5% resulted in clearly irritant partially pustular test reactions in up to 50%. Biopsies showed a purely neutrophilic infiltrate at 48 h, which was interpreted as an innate reaction rather than a true contact sensitization mediated by T cells. The decrease to manganese 2% resulted in a considerably lower number of irritant reactions. In a study of the Swiss Contact Dermatitis Research Group (SCDRG) on 609 patients, 13.9% still had a positive test reaction [22], and similar results have been observed in another study on patients with total hip replacements [35]. This irritant potential is also supported by a recent in vivo and in vitro study [4], demonstrating the irritant potential of several manganese oxides, e.g., manganese(II) oxide 2.5% in pet. still showed a considerable irritant potential. Therefore, positive patch test reactions to manganese and their relevance must be interpreted with the utmost caution.

35.2.11 Molybdenum

35.2.11.1 Properties and Occurrence

Molybdenum is an essential trace element and is used in cobalt chromium alloys to increase stability and to increase resistance to heat and corrosion.

35.2.11.2 Test Conditions

- Ammonium molybdate 1% aq. [18, 22]
- Molybdenum 5% pet. [7, 22]
- Molybdenum(II) chloride 1% aq. [21]
- Molybdenum(V) chloride 1% aq. and 0.5% pet. [8, 40]

35.2.11.3 Clinical Observations

In a series of 193 patients with contact dermatitis, 12 had a positive test reaction [8]. In 131 patients with coronary stents, 4 had positive test results [40]. There were no control groups, and relevance was not established. In a study of patients with metal implant complications, two positive tests were found [45]. In our series of 87 patients tested with molybdenum 5% pet. and ammonium molybdate 1% aq., no positive reactions were observed. In a study of the Swiss Contact Dermatitis Research Group (SCDRG) on 609 patients, only 0.3% had a positive test reaction to ammonium molybdate 1% aq. [22]. It remains to be established if molybdenum is a relevant contact allergen.

35.2.12 Niobium

35.2.12.1 Properties and Occurrence

Niobium is a soft, gray, ductile heavy metal. It is often used in steel alloys and in titanium alloys for orthopedic implants, e.g., in titanium-aluminum-niobium alloys.

35.2.12.2 Test Conditions

– Niobium(V) chloride 1% and 2% pet. [7, 22]

35.2.12.3 Clinical Observations

To our best knowledge, no unanimously proven case of contact allergy to niobium has been published; however, a female patient with intolerance to dental crowns with an unusual test reaction to niobium is presented in another chapter of this book (Chapter 11). In our preliminary assessment of 86 patients, niobium chloride 1% pet. was positive in 5%. However, in the multicenter study of the SCDRG, niobium chloride 1% pet. was positive in 2.8% [22], and clinical relevance could not be established. As with other unusual metals, test salts and concentrations should be verified. It remains to be established if niobium may induce sensitization and cause clinically relevant allergic contact reactions.

35.2.13 Potassium

35.2.13.1 Properties and Occurrence

Potassium is a silvery, shiny metal which is highly reactive with air and belongs to the essential trace elements. It is widely used in chemistry and medicine.

35.2.13.2 Test Conditions

– Potassium bromate 5% aq. [7]
– Potassium carbonate 1% aq. [7]
– Potassium chlorate 1% aq. [7]
– Potassium chloride 0.3% aq. [46]

35.2.13.3 Clinical Observations

A nurse was described to develop hand eczema after contact with a 15% solution of potassium chloride. Patch test with potassium chloride 0.3% aq. was positive; 20 controls were negative [46].

35.2.14 Rhodium

35.2.14.1 Properties and Occurrence

Rhodium is a silvery, shiny, chemically inert metal. It is used in alloys with platinum and as a protective cover for silver and white gold and in automotive catalysts, catalysts in the chemical industry, thermocouples, and the electronics and glass industries [6, 47].

35.2.14.2 Test Conditions

– Hexachloroiridate 0.1% aq. [5, 6]
– Rhodium chloride 1% aq. and 3% pet. [7, 22, 24]
– Rhodium sulfate 0.05% aq., 2% in undetermined vehicle [5, 6, 41, 48, 49]

35.2.14.3 Clinical Observations

Rhodium chloride 3% pet., as was previously used in a series of 110 patients, did result in positive test reactions in up to 32%, of which at least half were considered irritant. Currently, we use rhodium chloride 2% pet.; in our observation, it has still an irritant property and is often positive together with manganese chloride and vanadium chloride, possibly indicating an inherent irritant property of these three metal chlorides. In a study on 720 patients with eczema tested with rhodium chloride 1% aq., 2 patients had positive reactions with a potential relevance [50]. Some occupational cases with contact dermatitis have been reported, e.g., in a male goldsmith a positive test reaction was observed, whereas ten controls were negative [6]. A 59-year-old female goldsmith suffered from eczema on her fingers and arms; a positive test reaction to rhodium sulfate 2% was observed, and wearing of protective gloves resulted in amelioration [49]. Another two cases were observed of patients working with jewelry who were sensitized to rhodium chloride 1% aq. [47].

35.2.15 Rubidium

35.2.15.1 Properties and Occurrence

Rubidium is a soft, silvery, shiny alkaline metal which can spontaneously ignite upon exposure to air. It may be alloyed with mercury and is also used in alloys with gold and cesium.

35.2.15.2 Test Conditions

– Rubidium iodide 1% pet. [51]

35.2.15.3 Clinical Observations

A patient developed severe eczema on the face after application of rubidium-containing eye drops. The patch test with rubidium iodide 1% pet. was positive, while 20 controls were negative [51]. It was not elucidated whether another component of the eye drops could be responsible for the eczema, and no other cases have been reported so far.

35.2.16 Ruthenium

35.2.16.1 Properties and Occurrence

Ruthenium belongs to the group of platinum metals. It is used, among other things, as catalysts, in the production of jewelry, and in dental alloys.

35.2.16.2 Test Conditions

- Ruthenium 0.1% pet. or powder [7]
- Ruthenium oxide 2% pet.

35.2.16.3 Clinical Observations

So far, there have not been any bibliographical references of patients with contact dermatitis to ruthenium. Patch testing with ruthenium 0.1% pet. or in powder form can trigger contact urticaria [7].

35.2.17 Selenium

35.2.17.1 Properties and Occurrence

Selenium exists in the forms of red, black amorphous and gray metallic selenium and behaves like a half-metal. It is also an essential trace element. Selenium is used in the electronic industry, in glass and ceramics, and as a catalyst and accelerator in rubber products [5, 52].

35.2.17.2 Test Conditions

- Selenium sulfide 2% or 3% pet. [7]
- Sodium selenite 0.1% aq. [5] or pet. [52].

35.2.17.3 Clinical Observations

Selenium salts can be irritant or even toxic to the skin, and chemical burns may occur. After the handling of culture-medium containing sodium selenite, a lab technician developed hand dermatitis, airborne dermatitis, conjunctivitis, and asthma. Patch tests with sodium selenite 0.1% aq. were positive, and 15 controls were negative [5]. Four employees exposed to barium and sodium selenite in the glass industry suffered from dermatitis and/or conjunctivitis. In two employees an irritant pathogenesis and in the other two an allergic contact dermatitis with positive patch tests with sodium selenite 0.1% in pet. were reported [52]. Another occupational case of hand dermatitis with a positive patch test up to a dilution of 1:1000 sodium selenite was reported, and exposed controls were negative [53].

35.2.18 Silicon and Silicone

35.2.18.1 Properties and Occurrence

Silicon is one of the most common elements in the environment. It belongs to the half-metals and is commercially mainly used in solar panels and in explosives. Sodium silicate, known as "water" or "liquid glass," is widely used in industrial applications. Silicones, or polysiloxanes, are polymers made up from alternating silicon and oxygen atoms. They are typically inert, rubber-like, and heat-resistant and are used in sealants, adhesives, lubricants, medicine, cooking utensils, and insulations.

35.2.18.2 Test Conditions

- Silicic acid 5% pet. [54]
- Silicon tetrachloride 2% pet. [55] and 2% aq. [18]
- Silicone [56]

35.2.18.3 Clinical Observations

Silicon may induce granulomatous reactions. Several patients with infiltrated plaques or contact dermatitis at the site of a pacemaker implantation were reported. A 2-year-old child with a cochlear implant developed persistent pruritic erythema and discharge from the ear. He had a positive test result to silicone NSR-30 but not to silicone LSR-70 [56]. A 12-year-old girl with

pacemaker failure had a positive test to a manufacturer's patch; all tests with the single components were negative [57].

A 57-year-old man with recurrent ulcerative lesions, chronic eczematous changes, and contact urticaria resulting from contact with silicon has been reported, with an irritant patch test and a positive scratch test with sodium silicate [58]. Another case with contact sensitivity to silicic acid in an ointment (Unguentum Merck) has been observed; patch tests were positive with silicic acid 5% pet., and controls were negative [54]. Finally, gingival hyperplasia from silicium-containing dental cement with a positive test to silicon tetrachloride [55] has been reported. However, in a series of 30 patients with contact stomatitis, 10 had an irritant test to silicon tetrachloride 2% aq. [18].

35.2.19 Silver

35.2.19.1 Properties and Occurrence

Silver is a shiny, soft valuable metal. It is the most commonly used noble metal [6]. It is mainly used in the electronic industry, but also in jewelry, in dental alloys, and in topical medications. It may cause argyria upon prolonged topical or systemic exposure [59].

35.2.19.2 Test Conditions

- Silver bromide 2% pet. or aq. [7, 8]
- Silver chloride 1% with sodium thiosulfate [5, 6]
- Silver, colloidal 0.1% pet. [7]
- Silver fulminate 0.1% or 1% pet. [6, 7, 60]
- Silver nitrate 1% or 10% aq. and pet. [5, 61, 62]
- Silver sulfadiazine 5% pet. [7]

35.2.19.3 Clinical Observations

Although silver products are widely used in wound care for their antimicrobial properties, contact dermatitis due to silver, e.g., silver sulfadiazine, has only been rarely confirmed so far. In one patient, contact dermatitis developed after treating a burn, and a patch test with silver nitrate 1% aq. was positive [63]. On the other hand, 12% of 75 patients with leg ulcers and contact dermatitis had a positive test to silver nitrate 5% compared to 3.6% of patients without ulcers [64].

Some cases mostly related to occupational exposure to silver compounds with contact allergy from silver have been reported. Interestingly, often only aged 10% silver nitrate was positive, but not a freshly made solution [61].

A postal worker developed erythema upon contact with pure silver; a patch test with silver nitrate 1% in pet. was positive. A medical technician had lichenoid papules after contact with metallic silver; patch tests with silver chloride 1% and silver nitrate 1% aq. were positive. A jeweler with hand dermatitis and a positive patch test to silver nitrate 0.5% aq. has also been described [65].

A 42-year-old man with chronic hand dermatitis developed a positive reaction to a skin-marker pen containing 10% silver nitrate. A patch test with silver nitrate 1% in pet. was positive [62]. A patient receiving a solution containing protein and silver oxide for the treatment of nasal and oral pharyngeal ailments developed an immediate-type reaction. Scratch and intradermal tests with a solution 1% aq. were strongly positive. The eliciting agent was not further elucidated. Further cases are summarized in the overview article of Group and Lea [61].

A woman with chronic periodontitis from silver-amalgam fillings, contact dermatitis to silver jewelry, and a positive patch test to silver nitrate was reported [66]. She was cured after the removal of all silver-amalgam fillings.

The explosive silver fulminate may cause a pruritic often irritant exanthema [60]. In occupationally exposed workers, patch tests with silver fulminate 1% were positive; however, silver nitrate was negative in all. Because also many controls were positive, an irritant and allergenic potential of silver fulminate was thought to be likely [60].

35.2.20 Tin

35.2.20.1 Properties and Occurrence

Tin is a silvery, shiny soft metal. It is used for kitchen utensils and as a soldering agent [6].

35.2.20.2 Test Conditions

- Tin (metal) pure and 2.5% and 50% pet. [5–7, 9, 22]
- Tin(II) chloride 0.5% pet. [22]
- Tin(IV) chloride 10% aq. [21]
- Tin oxide 2% pet. [7]

35.2.20.3 Clinical Observations

From a series of 73 patients sensitized to nickel, 6 had also a positive patch test with metallic tin [67]. A metalworker developed an airborne contact dermatitis on the face after working with a metal alloy containing tin. The patch test with tin(II) chloride 0.5% and 1% pet. was positive. In a patient with systemic contact dermatitis from dental fillings, tin chloride 1% and zinc chloride were positive; the test with tin was estimated as clinically irrelevant [68]. Otherwise, tin appears to be an extremely rare contact allergen, as no further cases have been reported so far.

35.2.21 Tungsten

35.2.21.1 Properties and Occurrence

Tungsten is a transition metal with a very high density, durability, and a very high melting point [38, 39]. It is used in steels and has been formerly used in filaments.

35.2.21.2 Test Conditions

- Sodium tungstate 5% pet. [69]
- Tungsten (metal) 5% pet. [22]

35.2.21.3 Clinical Observations

There are no clearly documented cases of contact allergy to tungsten. In a series of 853 workers from a tungsten-processing plant, no positive test reactions were observed. However, 2% showed pustular lesions [69]. A 25-year-old hard metal-worker with asthmatic reactions to metal dusts showed a positive scratch test to pure tungsten and several tungsten compounds [70].

35.2.22 Uranium

35.2.22.1 Properties and Occurrence

Uranium is a very dense and relatively soft, radioactive heavy metal. It is mainly used in nuclear power plants and nuclear weapons [6].

35.2.22.2 Test Conditions

- Calcium uranate 2% in undetermined vehicle [5, 6]
- Sodium uranate 2% in undetermined vehicle [5, 6]
- Uranyl acetate 0.25%, 2.5%, and 25% in pet. [71]

35.2.22.3 Clinical Observations

Two patients developed hand dermatitis while working with uranium. Patch tests with sodium uranate 2% and calcium uranate 2% were positive [5].

Forty Gulf War veterans with skin problems exposed to depleted uranium were tested for skin reactivity to metals by patch testing with an extended metal series and uranyl acetate (0.25%, 2.5%, and 25%). A control comprised 46 patients. Only irritant reactions were observed [71].

35.2.23 Vanadium

35.2.23.1 Properties and Occurrence

Vanadium is a hard, ductile, and malleable heavy metal with similar properties as titanium. It is also an essential trace element [38, 39]. It is used in different alloys, particularly in orthopedic implants such as titanium-aluminum-vanadium alloy.

35.2.23.2 Test Conditions

- Vanadium (metal) 5% pet. [22]
- Vanadium(III) chloride 1% pet. [72]
- Vanadium(V) oxide 10% pet. [7, 9]

35.2.23.3 Clinical Observations

In a series of 239 patients who had problems with orthopedic implants, 5 had a positive reaction to vanadium [45]. In 126 enamellers and decorators, 1 patient with a positive test reaction to vanadium(V) oxide 10% has been reported [9]. In a small series of 14 patients, 3 female patients had a positive reaction to vanadium chloride 1% in petrolatum [72].

Vanadium chloride may often result in irritant reactions, as has been the case in our own observation. It is often associated with positive reactions to manganese chloride and rhodium chloride. This raises the question of whether it is not more likely the chloride moiety that is responsible for these weak reactions with typically a clear decrescendo evolution, indicating an irritant reaction.

35.2.24 Zinc

35.2.24.1 Properties and Occurrence

Zinc is a brittle, whitish-blueish metal which is also an essential trace element. It is mainly used in galvanic techniques, e.g., zinc coating/galvanizing of steel. It is also used in small amounts in dental prostheses and in medicine as a topical medicament in the form of zinc oxide, as well as a photo-protective substance.

35.2.24.2 Test Conditions

- Zinc 2.5% pet. [7, 22]
- Zinc chloride 2% aq. or pet. [8, 18, 21]
- Zinc oxide 1% aq. or 10% pet. [5, 7]
- Zinc peroxide 10% pet. [7]
- Zinc stearate 10% pet. [7]
- Zinc sulfate 1% and 2% pet. [5]

35.2.24.3 Clinical Observations

Contact allergy has been described in a 59-year-old patient with palmoplantar pustulosis who was positive to zinc chloride 2%. After restoration of her dental prostheses with zinc-free alloys, she became symptom-free [73]. Allergic contact stomatitis has been observed in one patient with positive test results to zinc oxide 1% in aqueous solution [5]. A 70-year-old patient had oral lichen planus and a positive patch test to zinc chloride 5% and 2% in petrolatum. After removal of her zinc-containing dental alloys, the oral lesions healed [74]. In several patients with dental fillings, an often pustular systemic contact dermatitis with positive patch tests to zinc has been reported [68]. In one female with disseminated eczematous lesions, a strongly positive patch test to zinc chloride and a positive lymphocyte proliferation test was present. A zinc-restricted diet led to gradual improvement upon alimentary re-exposure to a flare-up [75]. No controlled exposure and no serum zinc levels have been performed.

35.2.25 Zirconium

35.2.25.1 Properties and Occurrence

Zirconium is a soft, silvery, shiny heavy metal. It is mainly present in the form of zirconium oxide and is considered to be chemically inert. Together with aluminum oxide and titanium oxide, it belongs to the group of ceramics. It is used mainly in dental materials and orthopedic knee implants. It is also used in the electrotechnics industry and in ceramics, dyes, and deodorants. In bone cement, it is applied as a radiocontrast medium compound.

35.2.25.2 Test Conditions

- Sodium zirconium lactate 1% aq. [5]
- Zirconium 0.01% aq. [7]
- Zirconium(IV) chloride 1% pet. [22]
- Zirconium oxide 2% and 4% in “lotion” [5]
- Zirconium oxide pure and 0.1% pet. [7, 9]

35.2.25.3 Clinical Observations

Zirconium is a very inert material and has not been reported to cause contact sensitization or contact dermatitis. However, it may induce granulomatous reactions, e.g., upon the use of zirconium oxide in deodorants [5]. It has been also used as a protective layer on metal implants in metal-sensitized patients. Zirconium compounds have been used to prevent poison ivy dermatitis.

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Part VI

Metal Allergy in Select Patient Populations

Metal Allergy and Hand Eczema

36

Richard Brans and Swen M. John

36.1 Hand Eczema

Hand eczema is a common, non-infectious skin inflammation restricted to the hands with a 1-year prevalence of approximately 10% [1, 2]. Women are twice as often affected than men. Both individual and environmental factors are involved in the pathogenesis of hand eczema [3]. Subtypes include irritant and allergic contact dermatitis, atopic dermatitis, mixed forms and minor groups with vesicular and hyperkeratotic hand eczema [4–6]. The single most common endogenous risk factor for hand eczema is atopic dermatitis [7–9]. In patients with atopic dermatitis, the hands are frequently involved, while the likelihood of developing irritant contact dermatitis is significantly increased [10–12]. Due to manual work, occupational hand eczema is very common and one of the most frequent occupational diseases [4]. However, the hands could also be exposed to hazardous substances during leisure time. Often, it is difficult to identify the cause of hand eczema, as mixed exposures to skin irritants and contact allergens at home and at work, as well as individual predispositions, interact with each other.

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36.2 Hand Eczema and Metals

Hand eczema can be caused or aggravated by manual exposure to metals. However, the level and frequency of exposure to metals differ between individuals, mainly depending on occupational and spare-time activities. Isolated irritant contact dermatitis of the hands caused by metals is very rare and may be related to metal dust or rough metal surfaces (e.g. in the metal industry or in dental technicians). Metal-induced allergic contact dermatitis of the hands is probably more frequent. Its diagnosis is based on the outcome of patch testing and information on exposure to a specific metal in the patient's environment. A positive patch test could be related to a past exposure or allergic contact dermatitis on body areas other than the hands. Thus, a thorough investigation of its relevance for hand eczema is crucial. Nickel, cobalt and chromium are the most important metal contact allergens. The level of exposure to these metals has considerably changed over time due to regulations, changes in consumer products or improvements in work hygiene and technical development. Thus, some contacts to metals that used to be relevant for inducing allergic contact dermatitis of the hands in the past, may not be problematic anymore. However, some significant exposures to metals have remained, while other new exposures arise.

To assess the relevance of contact to metals for hand eczema, it is important to measure how much metal is released from handled items and

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how much of it is deposited onto the hands when different manual tasks involving metal-containing items are performed. The release of metal ions from items depends on a variety of factors related to the item itself and the environment. Alloys can have inherent properties very different from those of the metals they contain [13]. Thus, metal ion release from an alloy is not directly correlated to the level of metal content in the alloy. Surface finish such as polishing and coating of the item can prevent or reduce metal release, especially in new, unused consumer products. In contrast, corrosion or deterioration of coating following use and wear may result in increased metal ion release [14]. Environmental factors involved in metal ion release include pH, temperature and relative humidity [15]. Moreover, the frequency and duration of exposure to a metal item affect the amount of metal accumulated on the skin. Apart from techniques using artificial sweat, spot tests are available for screening purposes to determine the release of metal ions from individual items, such as the cobalt spot test [16], the dimethylglyoxime (DMG) test for nickel [17] or the diphenylcarbazide spot test for hexavalent chromium [18]. For the assessment of nickel, chromium and cobalt deposited on the hands, acid wipe sampling [19–22] and a finger immersion technique have been established [23, 24]. Recently, also the DMG test was proposed for visualisation of nickel deposits on the hands [25].

Even if metal release from an item and its deposition on the hands is detected, its relevance for hand eczema is still unclear, as the threshold level of metals that is needed to elicit allergic contact dermatitis in sensitised individuals is difficult to determine and may vary. First, metal ions have to pass the stratum corneum in order to reach the viable layers of the epidermis and activate the immune system. The skin of the palms is characterised by a thick stratum corneum which may prevent or inhibit the passage of metal ions [26]. In contrast, sweating and occlusion may promote their permeation [27, 28]. Experimental nickel dose-response studies have shown that the reactivity of the hands and fingers in nickel-sensitive individuals is probably of the same magnitude as reactions on other skin sites [15, 29]. However, endogenous factors may be involved in the individual risk to develop allergic contact dermatitis, such as an increased immune reactivity or an impaired skin barrier function [30]. Recently, it was reported that null mutations in the filaggrin gene are associated with nickel allergy and related contact dermatitis [31, 32]. Moreover, mechanical strain during manual work or concomitant exposure to irritants could increase the likelihood of developing allergic contact dermatitis [33]. In conclusion, assessing the relevance of metals for hand eczema is often difficult and requires a thorough and individualised investigation.

36.3 Nickel

Contact allergy to nickel is very common, affecting about 17% of women and 3% of men in the general population [34]. For the past decades, ear piercing and wearing of nickel-releasing costume jewellery have been the primary routes of sensitisation [35, 36], explaining the higher prevalence in women. Therefore, nickel allergy is usually nonoccupationally acquired [37]. In 1994, a nickel regulation was passed in the European Union (EU) to protect European consumers from excessive nickel exposure (1994/27/EC). The EU Nickel Directive came into full force in 2001 [38, 39] and has become part of the EU chemical regulation REACH since 2009. The directive limits nickel release from items in prolonged contact with the skin, e.g. jewellery, watches, buttons and zippers. From 2009 on, even mobile phones were included in the directive [40]. This led to a decreasing trend regarding the occurrence of nickel allergy, in particular in young women [41–45]. However, in many countries outside the EU, no regulation on nickel exposure exists, and even within the EU, nickel allergy is still frequent, suggesting that there are still several items on the market, including jewellery, that release nickel [46, 47]. In addition, there are several nickel-releasing items that come in brief and repeated contact with the skin that are not covered by the EU Nickel Directive, such as tools, keys, laptops and coins [48, 49].

Assessment of the role of nickel in causing hand dermatitis has been complicated. It is not uncommon to find nickel allergy on patch testing, but it is difficult to determine whether this is of relevance for hand eczema or simply a reflection of past exposure to nickel-releasing jewellery or other non-manual nickel exposures [24]. Early epidemiological population-based studies indicated that nickel allergy is associated with hand eczema, especially in women [50–52], which was supported by a twin study [8]. Some described a particular association with vesicular hand eczema [53, 54], which was, however, not confirmed by others [55]. More recent epidemiological studies show that previous associations between nickel allergy and hand eczema disappeared after introduction of legislations to decrease exposure to nickel in the general population [45, 56]. Thyssen et al. demonstrated that the prevalence of concomitant nickel contact allergy and a history of hand eczema decreased significantly among Danish women aged 18–35 years from 9.0% in 1990 to 2.1% in 2006 [45]. In a long-term follow-up of a cohort of Danish adolescents over 15 years, earlier results were refuted [57] as an association between incidence and prevalence of hand eczema and nickel allergy in childhood was no longer found [58]. Similarly, in a population-based 20-year follow-up study, nickel allergy in childhood did not increase the prevalence of hand eczema in women later in life [59]. When repeating patch testing in a subgroup of this cohort, only nickel-positive individuals without childhood eczema had a doubled risk for hand eczema [60]. However, even though recent epidemiological studies do not support a general association between nickel allergy and hand eczema, it is still possible that individuals with contact allergy to nickel develop allergic contact dermatitis of the hands when exposed to nickel. In a double-blind placebo-controlled study, a statistically significant aggravation of hand eczema was observed when the hands of patients with nickel allergy and low-grade hand eczema were exposed to 10–100 ppm nickel over 2 weeks [15]. However, this study did not provide information on the development of hand eczema in nickel-allergic patients without pre-existing dermatitis of the hands.

Nickel-releasing items could come in contact with the hands both at work and during leisure time. A great variety of exposures is possible and should be thoroughly investigated in individuals with hand eczema and a positive patch test to nickel. Possible spare-time exposures of the hands to nickel include mobile phones [47], equipment at the gym [61] or electronic cigarettes [62]. In many industrialised countries, the current occupational nickel exposure is different from the pattern of nickel exposure that was observed in the past. Nickel allergy was once common in the plating and metal industry. Now, it is much rarer due to improvements in workplace practices and changes in products. Therefore, a positive patch test to nickel is often not of occupational relevance [63, 64]. However, work-related exposure to nickel-releasing items still occurs and should be considered as potential cause of hand eczema in individuals with nickel allergy. A study by Lidén et al. in the late 1990s revealed that 27% of 565 hand-held tools on the Swedish market with metal parts that come into contact with the skin released nickel according to a DMG test [65]. While more recent Danish studies identified nickel release in only 5% of 200 unused hand-held work tools [66] and in only one of 200 scissors from random hairdresser salons [67], a recent study from Germany could not confirm this marked decrease and detected nickel release in 32.5% of hand-held tools (22.8% from the grip part) [68]. Thus, the exposure to nickel from tools and other metallic items may differ depending on the country as well as the type and origin of products and should be assessed individually. Nickel release was also reported for other items in contact with the hands during work, including keys [19], sewing needles of dressmakers [19], hooks of hairdressers [67], guitar strings [69], dermatoscopes used by dermatologists [70] and tools and alloys used by dental technicians [71, 72].

Following short and frequent skin contact with nickel-releasing items, nickel deposits can be detected on the hands [73]. Staton et al. found high levels of nickel on the fingers in nickel platers and nickel refinery workers but low levels in cashiers, shop assistants, bar staff and hairdressers

[24]. A study by Lidén et al. demonstrated that nickel is deposited on the hands in various occupations after normal work routines, e.g. locksmiths, carpenters and cashiers [22]. Other studies confirmed the deposition of nickel on the hands of locksmiths, metal workers and cashiers [20, 25]. Also, Gawkrodger et al. found considerable amounts of nickel on the fingers of nickel platers, cashiers, sales assistants and caterers [23]. Jensen et al. detected nickel on the hands of six patients with vesicular hand eczema after performing their normal work routines for 2 h involving handling of nickel-releasing items (e.g. keys, sewing needle) [19]. They reported that nickel-reducing measures led to complete symptom relief in all cases. Deposition of nickel was mainly detected on the first three fingers of the dominant hand [19, 20, 22, 74]. Much lower levels were found on the palms and on the back of the hands. Thus, the distribution of eczema lesions should be considered when suspecting metal exposure as a potential cause of hand eczema [75]. Lesions predominantly located in areas of prolonged or repeated direct contact to nickel-releasing items may be indicative of nickel-induced allergic contact dermatitis.

The majority of coins worldwide consist of a copper/nickel alloy and release nickel. Thus, coins are another source of nickel exposure, e.g. coinage from the UK, Sweden and euro coins [74, 76–78]. It was demonstrated that handling of nickel-releasing coins results in deposition of nickel on the skin, especially on the volar aspects of the fingertips [24, 74, 79]. This could be of particular importance for nickel-allergic individuals in occupations in which coins are repeatedly handled. In accordance, deposition of nickel on the hands of cashiers and related occupations has been demonstrated [22–25]. However, it is unclear whether occupational exposure to nickel from coins is relevant for hand eczema [24]. An experimental study in which nickel-releasing coins were handled by nickel-sensitive individuals without hand eczema had a negative outcome [80]. In contrast, Gawkrodger et al. demonstrated that the levels of nickel deposited on the skin of individuals working in different occupations, including cashiers and sales assistants, were high enough to induce allergic contact dermatitis in some nickel-allergic subjects in a single-open application test [23]. Individuals with a strong sensitisation to nickel may be particularly at risk to develop allergic contact dermatitis from the handling of nickel-releasing coins as they may react already to small amounts of metal ions deposited on the skin. Gradual patch testing with different concentrations of nickel ('titration') may help to identify subjects with such a strong sensitisation.

Apart from direct skin contact to nickel, other putative pathomechanisms of nickel-induced hand eczema have been described, such as hand eczema resulting from transcutaneous absorption of nickel from, e.g. earrings [81]. Others have reported systemic allergic contact dermatitis primarily involving the hands following nickel ingestion. In particular, vesicular hand eczema or pompholyx in nickel-sensitive individuals has been connected with oral nickel uptake. However, the data on this subject is very controversial [82, 83].

36.4 Cobalt

Relevant exposures to cobalt are less understood than for nickel and chromium. Cobalt is found in different corrosion-resistant alloys, magnetic alloys and hard metals; in orthopaedic and dental prosthetics, as a pigment in pottery, glass, leather and paints; in cement; and in cosmetic products, detergents, cleaners and various other applications [84, 85]. In the past, metal items such as costume jewellery often contained both nickel and cobalt, which may explain the high frequency of concomitant patch test reactivity to nickel and cobalt [86, 87] and the higher frequency of cobalt allergy in women [34, 87]. Nowadays, leather products might be an important source of cobalt release [88] and induction of allergic contact dermatitis in sensitised individuals [89]. In contrast to nickel and chromium, so far no regulation exists to limit exposure to cobalt. Cobalt allergy is frequent, affecting 5.2–8.8% of patch-tested patients [87, 90]. However, its clinical relevance is often unclear [85], while false-positive patch test reactions are common [91–93].

Occupational allergic contact dermatitis of the hands caused by cobalt has been observed in hard metal workers, metal workers, cement workers and pottery workers [91, 94–96]. Also, dental technicians are at risk [85]. However, even though hard metal alloys often contain cobalt in concentrations of about 10%, the prevalence of cobalt allergy in metal workers is low [91]. In the past, isolated sensitisations to cobalt were suggested to be likely acquired at work as they were often seen in hard metal or pottery workers [91, 95]. A recent study, however, demonstrated that isolated cobalt allergy is less associated with occupational dermatitis and hand eczema than patch test reactivity to cobalt in combination with other contact allergies. Nowadays, it is equally found in men and women and across age groups [85].

Cobalt release from metal items is less frequent than nickel release and has been demonstrated for jewellery, hair clasps and non-professional work tools [16, 97, 98]. It was shown that several cobalt-containing hard metal alloys stored in synthetic sweat for 1 week released cobalt in concentrations high enough to elicit allergic contact dermatitis in cobalt-allergic individuals [99]. Also, tools and alloys handled by dental technicians release cobalt [71]. In addition, it was demonstrated that occupational contact with hard metal alloys, e.g. as part of tools, results in cobalt deposition on the hands [20, 21, 100]. Thus, handling of cobalt-containing hard metal alloys may cause hand eczema. However, Nielsen et al. reported that it is more difficult to elicit allergic contact dermatitis on the hands in cobalt-allergic patients than in nickel-allergic patients when exposed to the respective allergen in experimental settings [15, 101]. This may indicate that cobalt allergy is not often relevant for hand eczema. Moreover, both in a Danish and in a German study, hardly any cobalt release was found recently when testing hand-held work tools with the cobalt spot test [66, 68]. It should be noted that only unused tools were investigated and, therefore, no conclusion can be drawn regarding cobalt release after wear and use of such tools. Yet, exposure to cobalt from tools or other items should not be overestimated, but individually assessed when a relevance for hand eczema is suspected in cobalt-allergic individuals. This is, for example, supported by the case of a baker who developed allergic contact dermatitis of the hands following occupational exposure to cobalt-releasing baking sheets [102].

36.5 Chromium

Chromium is found in metals, cement and leather, as well as paint and plywood. Hand eczema related to chromium allergy has been primarily associated with exposure to cement due to its content of hexavalent chromium [103]. Hand eczema has been commonly diagnosed in construction workers and is associated with a very persistent course [104]. In 2005, an EU Directive came into effect restricting the marketing and use of cement containing >2 ppm of water-soluble hexavalent chromium, its implementation achieved by adding ferrous sulphate to cement in order to keep the concentration of hexavalent chromate low. In Europe, this has led to a decrease of chromium allergy and dermatitis, particularly in men [105] and in the building trade [106]. However, in other parts of the world, a comparable regulation has not been adopted and, therefore, chromium-containing cement continues to be an important cause of hand eczema [107]. Even in the EU, occupational chromium allergy still occurs despite the regulation, e.g. due to lack of work hygiene [108].

In recent years, the prevalence of chromium allergy is rising again within the EU. This has been primarily attributed to leather, which is frequently tanned with chromium sulphates and has become the most common cause for chromium allergy in industrialised countries [105, 109–111]. Leather shoes are probably the most important source of chromium exposure resulting primarily in allergic contact dermatitis of the feet. However, workers in the leather industry are also at risk to develop occupational hand eczema from contact to chromium. Moreover, allergic contact dermatitis of the hands caused by chromium-containing leather gloves has been reported [112, 113]. The release of chromium from leather depends on various environmental factors, such

as pH, temperature, relative humidity, sweating and exposure time [114, 115]. Since May 2015, leather products that come into contact with the skin have been regulated in the EU, limiting their content of hexavalent chromium to <3 ppm [Commission Regulation (EU) No. 301/2014 amending annex XVII of EG 1907/2006 (REACH)] [116]. The future will show if this regulation is effective in reducing the impact of chromium allergy.

Apart from leather, metals, such as in tools and alloys used by dental technicians, may also release relevant amounts of chromium and induce hand eczema [71]. Only a few studies have assessed the deposition of chromium ions on the skin. Bregnbak et al. detected chromium on the hands after a short exposure to samples of leather and metal [117]. Similarly, Lidén et al. reported deposition of chromium on the hands of 18 workers (carpenters, locksmiths, cashiers and secretaries) after 10–180 min of normal work, including exposure to metallic items [22]. Similarly to the other metals, no threshold level is known for chromium to induce allergic contact dermatitis of the hands. However, direct exposure to chromium-releasing items should be avoided in individuals with chromium allergy and hand eczema to avoid triggering of the disease.

36.6 Other Metals

Hand eczema caused by other metals is rarely reported despite a wide distribution of these metals in the environment. The reported rate of contact allergy to gold sodium thiosulphate in patch-tested patients differs in various countries [118]. Usually, no clinical relevance can be obtained. Accordingly, a positive patch test to gold sodium thiosulphate was not considered relevant to hand eczema in Swedish dentists [119]. However, cases of hand eczema induced by gold jewellery may occur [120]. The sensitising capacity of silver is controversial. Accordingly, case reports on allergic contact dermatitis of the hands caused by silver are very rare [121]. The use of mercury has been banned or restricted for many applications in most countries due to its toxic capacities. Only a few cases of occupational allergic contact dermatitis from mercury have been reported [122]. Also, dental restoration with amalgam has become uncommon in modern dentistry, and with proper practices, it should not be problematic for the dentist to avoid skin contact [119]. Palladium is increasingly used in dental alloys, in the telecommunication industry and jewellery. However, the relevance of positive patch test reactions to palladium is usually unclear because of its frequent co-sensitisation with nickel [123]. Only a few cases of occupational contact dermatitis from palladium have been reported [124, 125]. Other metals, such as copper and aluminium, are considered very weak skin sensitisers, and contact allergy to these metals is rarely diagnosed.

36.7 Conclusions

Hand eczema can be caused or aggravated by metals, especially in the occupational setting. In particular, metal-induced allergic contact dermatitis of the hands should be considered in individuals with metal allergy. The most important metal allergens are nickel, cobalt and chromium. The level and type of exposure to these metals have substantially changed over time and differ between countries. Thus, if a metal is suspected as a possible cause of hand eczema in sensitised individuals, a thorough investigation is required to assess the specific metal exposure and its relevance. Once a relevant exposure to a metal-releasing item is established, measures to prevent or reduce direct skin contact should be promoted, such as replacement of the item or covering of metal-releasing parts of the item which are in direct contact with the hands (e.g. handles). In addition, wearing of protective gloves when handling the item or other improvements of work hygiene, including automation, can be effective interventions.

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Metal Allergy in Children

37

Chandler Rundle, Nikoleta Brankov, and Sharon E. Jacob

- Genetic and environmental triggers contribute to atopic dermatitis and allergic contact dermatitis (ACD), both of which are common in children.
- The risk factors for developing ACD from metals consist of skin barrier defects (filaggrin mutations), impaired barrier function, and immature barrier function.
- The epidermis has a pH buffering system that creates a favorable environment for hapten production, which leads to increased rates of allergen sensitization.
- Nickel is the most commonly detected allergen worldwide in patients of all ages.
- ACD caused by nickel can dramatically affect quality of life.
- *Staphylococcus aureus* infections destroy filaggrin-deficient keratinocytes and also increase the immune system susceptibility for ACD.

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37.1 Contact Sensitization and Atopic Dermatitis

Atopic dermatitis (AD) is a common skin disease especially in children that involves pruritus, erythema, and inflammation. In children above 2 years, the locations where it most commonly occurs are the face, neck, and flexor surfaces (knees, elbows) [1]. The pathogenesis of flexural eczema consists of a variability in children's skin thickness, pH, barrier function, moisture, warmth, and frequency of friction [2]. The most common risk factors that lead to a link between AD and allergic contact dermatitis (ACD) are skin barrier defects (filaggrin gene mutations) and impaired and immature barrier function [3].

The filaggrin structural protein has a critical role in maintaining the epidermal skin barrier, via, namely, hydration of the stratum corneum, production of acidic metabolites, and differentiation of all the skin layers [4]. A loss-of-function mutation in the filaggrin gene (*FLG*) leads to increased transepidermal water evaporation and reduced skin dehydration [5, 6]. Natural moisturizing factor (NMF) is a breakdown product of filaggrin that is important for retaining moisture in the skin. That said, NMF levels are low during the first year of life, and water storage and transport are attenuated [7]. Low NMF, in conjunction with *FLG* mutation, adds an additional factor by which the skin dehydrates. Additionally, filaggrin is a histidine-rich protein that chelates nickel ions, therefore preventing penetration of free

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nickel ions. Mutations in *FLG* (with subsequently lower levels of histidine residues) confer an inability to prevent penetration of nickel ions [8] and may in fact be a factor in increased absorption of substances by the atopic integument [9]. Notably, these mutations have a strong association with AD [9].

In addition, filaggrin is also important in that one of its functions is acidification via degradation and conversion into polycarboxylic acids [10]. When there is a mutation in *FLG*, there are less polycarboxylic acids formed, which leads to a less efficient skin buffer. If there is an increase in pH (less acidic) of the stratum corneum, this activates serine proteases, which are enzymes that solely degrade epidermal barrier proteins [11]. An increase in these serine protease enzymes provokes T helper (Th) 2 inflammation [12], and the more alkaline environment allows microbes, such as *S. aureus*, to grow and penetrate through the skin [13].

T-cell immune response to metal, nickel, for example, occurs as a consequence of nickel binding to a histidine residue, and as a result forming an antigenic epitope [3]. The equilibrium of nickel bound to histidine residues is a pH-dependent process [3]. Acidity of the skin results in dissociation of nickel ion from histidine residues and an inability to elicit an immune response. Alternatively, decreased acidity of the skin (due to *FLG* mutations) allows the equilibrium to shift toward the formation of nickel-histidine complexes that subsequently lead to a T-cell immune response [3]. Therefore, *FLG* mutations are multifaceted in that they provide multiple routes to predispose individuals to contact sensitization, specifically nickel [3].

Biofilms are bacterial communities enclosed by an extracellular matrix that promote bacterial growth and alter defensive host mechanisms [14]. The bacteria that live within these biofilms are found to be more resistant to antibiotics and also allow supercolonization of the bacteria. Biofilms also augment the inflammatory response [15], which leads to more aggravation of the AD condition. *S. aureus* also has the ability to incorporate metals by placing them into the skin's cellular compartments [16]. With *S. aureus*, polyphosphate bodies are responsible for binding and sequestering large amounts of the metal nickel during bacterial colonization [16]. The presence of *S. aureus* also represents a two-hit process to predispose individuals to nickel sensitization. Carriers of *S. aureus* have increased circulating interleukin-2 (IL-2), a characteristic cytokine of a Th1 response [3]. Subsequently, increased levels of inflammatory cytokines prime the immune system for nickel allergic contact dermatitis (Ni-ACD) [3]. Additionally, the release of alpha-toxin by *S. aureus* in individuals with *FLG* mutations decreases keratinocyte adhesion by selective destruction of keratinocytes, thus further compromising the skin barrier and allowing greater penetration by free nickel ions [3].

37.2 The Metals: Exposure and Evidence

37.2.1 Nickel

Children worldwide have a high prevalence of contact sensitization to nickel, upward of 25% of patch-tested children (Fig. 37.1). It is estimated that the combined indirect and direct costs for nickel allergy in the United States are as high as $5.7 billion per year [17]. Children can be

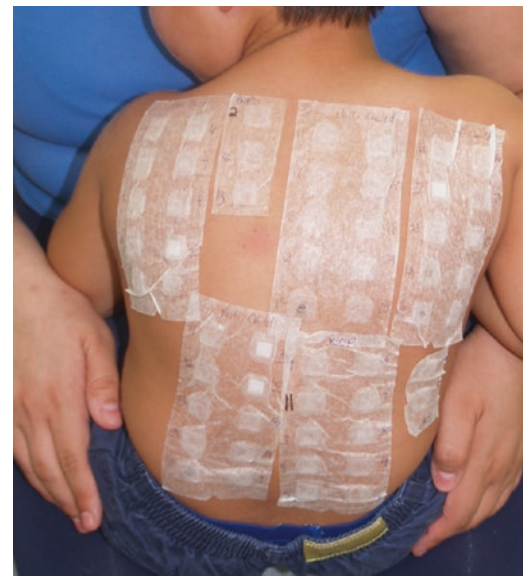

Fig. 37.1 Patch testing placement in a small child

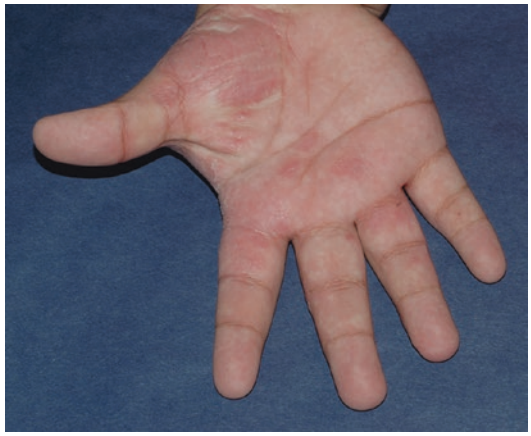

Fig. 37.2 Hand dermatitis in a child from handling toys and coins

Fig. 37.3 A teen reacting to a cell phone

sensitized via exposure to nickel in clothing snaps, coins, toys, electronics, belt buckles, and jewelry [17, 18] (Fig. 37.2).

There is expansive literature written on objects releasing nickel and other metal allergens (Table 37.1). In fact, over the last 30 years, there has been a significant increase in the amount of nickel sensitization. Highly prevalent, nickel sensitization is estimated to affect 28.1% of children in North America [3]. A recent article on objects containing nickel in the community sheds light on the prevalence of nickel in daily lives. However, the likelihood of different age groups encountering such objects varies. Infants ranging from newborn to 6 years of age are likely to become sensitized from nickel in piercings, adornments (belts, press studs), and toys [88]. Children ages 7 to 12 begin wearing more jewelry, have access to electronic tablets, or begin playing musical instruments—all of which potentially contain sensitizing agents [89]. In the teen years, children have further exposures through daily mobile phone use [59] (Fig. 37.3). The recent literature supports the potential role of toys in nickel sensitization. In a study by Jensen et al., 34.4% of toys purchased from the United States and Denmark tested positive for nickel release [90]. In fact, Overgaard et al. determined that after short-term play, nickel-containing toys deposited a clinically relevant amount of nickel (i.e., enough to risk nickel sensitization) [91].

Ni-ACD, a type IV hypersensitivity reaction, manifests as inflammation, itching, and eczema in sensitized individuals who come into contact with a substance that has a high release of nickel ions. Risk factors for contracting Ni-ACD include the female gender, young age, piercings, genetic susceptibility, and *FLG* mutations [3]. The work by Huber et al. evaluating 65 AD patients versus 78 controls (noneczematous) prospectively found a statistically significant association between skin barrier defects (*FLG* mutations), impaired and immature barrier function, and contact sensitization to nickel [92]. In fact, it has been suggested that nickel sensitization could be considered a minor criteria in AD [93].

Of interest, Pistoor et al. demonstrated that cross-reactivity can be divided into three groups: cross-reactivity with (1) copper, (2) palladium, and (3) no cross-reactivity [94]. The former two processes are likely due to the bivalency and respective positions on the periodic table with regard to nickel—suggesting a similar chemical profile to that of a nickel ion [94]. Clinically, exposure to either copper or palladium may elicit an immune response initially formed against nickel ions. Other metals, such as cobalt, chromium, and gold, are also capable of producing type IV hypersensitivity immune responses [95].

Table 37.1 Sources of exposure to selected metals

Nickel [19–37]	1. Earrings 2. Jewelry 3. Cosmetics 4. Cigarettes 5. Coins 6. Sunflower oil 7. Razors 8. Laptops 9. Orthodontics 10. Licorice 11. Guitar picks	12. Lottery scratch pads 13. Face painting makeup 14. Chocolate 15. Staples 16. Soy 17. Spirulina 18. Cell phones 19. Stainless steel 20. 18 k white gold 21. Keys
Cobalt [38–55]	1. Leather 2. Dark jewelry 3. Metal-on-polyethylene hip arthroplasty 4. B12 vitamin 5. Partial dentures 6. Blue eye shadow 7. Hard metal saw 8. Dental implants 9. Eyeglass frames	10. Coins 11. Pliers 12. Laptop 13. Glazed pottery 14. Cement 15. Acrylic nail art 16. Blue tattoo 17. Brazil nut 18. Liver 19. Cleaner and detergent
Chromium [43, 56–67]	1. Detergents and bleaches 2. Dentures 3. Broccoli 4. Mobile phones 5. Eye shadow 6. Leather goods 7. Wine 8. Paints and dyes 9. Hip prostheses 10. Tea and coffee	11. Tattoo ink 12. Hard tap water 13. Dietary supplements 14. Concrete 15. Tomatoes 16. CCA-wood deck 17. Stainless steel 18. Canned foods 19. Footwear
Palladium [68, 69]	1. Dental appliances 2. Chemical catalysts 3. Electrical appliances 4. Jewelry	5. Automotive emission control catalysts 6. Chemotherapy agents
Mercury [70–73]	1. Marine fish and seafood 2. Coal 3. Metal ores 4. Paint 5. Electronic devices 6. Chlor-alkali plants 7. Rice	8. Vegetables 9. Meat (not including poultry and fish) 10. Soil 11. Thermometers 12. Blood pressure cuffs 13. Amalgams
Cadmium [74–76]	1. Waste disposal 2. Phosphate fertilizers 3. Coal combustion 4. Iron and steel production 5. Zinc production 6. Sewage sludge	7. Batteries 8. Metal plating 9. Pigments 10. Plastics 11. Cigarette smoking 12. Tofu
Vanadium [77–79]	1. Skim milk 2. Lobster 3. Vegetable oils 4. Vegetables	5. Grains and cereals 6. Particulate matter 7. Industrial enterprises (contaminated air)

Table 37.1 (continued)

Copper [80–82]	1. Milk 2. Cold tap water 3. Legumes 4. Potatoes and potato products 5. Nuts and seeds 6. Beef 7. Fillers	8. Plating agents and surface treating agents 9. Batteries 10. Building/Construction materials 11. Electrical and electronic products 12. Food packaging
Platinum [83, 84]	1. Catalytic converters of modern vehicles 2. Antineoplastic drugs (cisplatin and carboplatin) 3. Airborne particulate matter	4. Soil 5. Roadside dust 6. Vegetation, river, coastal, and oceanic environments
Gold [85]	1. Dental gold	2. Jewelry
Silver [86, 87]	1. Medicinal use 2. Washing machines	3. Refrigerators 4. Drinking water

37.2.2 Cobalt

Cobalt exposure may be associated with jewelry, medical components and devices, and leather goods. Recent studies have demonstrated that cobalt is the second most common contact sensitizer (9.1%) in US children [96]. Cobalt is found in a different column in the periodic table compared to nickel, copper, or palladium, and thus cobalt does not cross-react with these. However, in vitro studies suggest concomitant reactivity to nickel and cobalt is more likely [97].

37.2.3 Chromium

Chromium is a metal for which uses are expansive. Ranging from industrial uses, jewelry, leather, and food content, chromium remains a prevalent sensitizer for the general population [98]. Chromium is a standard chemical included in the T.R.U.E. Test™ (SmartPractice, Phoenix, AZ). Among Polish children tested, 6.8% had a positive patch test to chromium; however, this study did not report the main source of chromium in children [99]. The most common source of chromium in children is leather [100, 101]. In children, sensitivity to chromium is largely responsible for shoe contact dermatitis [62].

37.2.4 Palladium

Palladium is a common metal used in industry, jewelry, and dentistry. However, it is speculated that palladium-associated allergies are the result of potential cross-reactivity with more allergenic metals, such as nickel—a common combination in the production of alloys. Although sensitization primarily occurs by contact with the metal, airborne palladium particulates associated with developed countries still pose a risk, albeit its low sensitizing potential (metallic or oxidic forms) [102]. In a 10-year study, Durosaro et al. reported that 110 out of 910 (12.1%) patients patch tested to palladium chloride 2% in petroleum were positive [103]. Their study confirmed a new finding, in that the degree to which gold co-reacts with palladium is similar to the known palladium cross-reactivity with nickel [103]. Therefore, an individual allergic to palladium may also experience symptoms/allergic reaction due to the presence of common allergenic species (nickel, gold) [103].

37.2.5 Mercury

Classically, mercury is known to have a high rate of sensitization. Kuljanac et al. presented that 6.2% of children were sensitized to mercury. Although this

study's results regarding mercury did not address if sensitization rates were correlated to vaccination, it did distinguish mercury as a prevalent childhood sensitizer [104]. Another study noted that mercury sensitization was largely related to mandatory vaccines, mercurochrome, an incidental broken thermometer, and topical drops [105].

Sensitization to mercury has been associated with the use of thimerosal (an organic mercurial) as an antiseptic in vaccines. It has also been demonstrated that 46% of patients tested were sensitized to thimerosal [105]. However, only 19.2% of the 125 patients tested presented with a positive intradermal reaction. The intramuscular injection of thimerosal resulted in only a mild local inflammatory reaction. That said, more than 90% of the allergic patients tolerated the intramuscular injection of thimerosal (which had a similar concentration of thimerosal to that present in vaccines). Intramuscular inoculation with a thimerosal-containing vaccine should not be contraindicated in patients who have a prior history of positive patch test to thimerosal, especially if the intradermal test is negative [105]. The intradermal test is used to confirm clinical suspicion for an allergen by unveiling false-negative metal reactions, helping to shed light on doubtful patch test reactions [106].

A 2-year study by Grandjean et al. demonstrated that there is a significant risk of contact sensitization and naturally acquired passive immunity during prenatal development—a window in which sensitization is influenced by the mother's diet [107]. This period of vulnerability is explained by the development of the immune system. Prenatally, Th2 functions are dominant, whereas Th1 responses take over in the postnatal period. This fundamental difference explains why sensitization to mercury is more prevalent prenatally (mother's diet) as opposed to postnatally (breast milk) [107].

37.2.6 Cadmium

Sensitizations to metals vary greatly with respect to the environment. Cadmium sensitization, for example, has been associated with prenatal exposure and subsequent AD susceptibility in infancy [108]. Sarasua et al. demonstrated that urine cadmium blood levels were associated with increased immunoglobulin (IgA, IgG, and IgM) and B cell circulatory volumes. While this study did not note immunosuppression as a result of cadmium exposure [109], studies have suggested that cadmium is capable of impairing secondary humoral responses [110] and therefore able to initiate a type IV hypersensitivity reaction through an imbalance of Th1 and Th2 cells. This is similar to how a decrease in levels of Th1 products and inconsistent upregulation in levels of Th2 products and negative regulators explain the general hyporesponsiveness in AD skin versus non-AD skin states [111].

37.2.7 Copper

Although it has been postulated that copper is a rare allergen considered to have low sensitizing potential, a 2001 study demonstrated that 3.53% of patients had a positive patch test (PPT) [112]. Commonly, reactions to copper will occur as a result of a cross-reaction with nickel or previous nickel sensitization (or cobalt in rare cases). In fact, one of three types of T cells isolated in a study conducted by Wöhrl et al. noted T cells that cross-reacted with nickel and copper [112]. Pulpitis has been reported as a presentation of ACD in children [113]. Of interest, die-cast model cars made from zinc, aluminum, magnesium, and copper alloy and 1p & 2p coins have been reported in association with pediatric ACD [113]. Copper contact sensitization has more frequently been reported in adults with occupational exposure, such as plumbing, dentistry, electronics, people working with machinery, and handling of coins [114, 115].

37.2.8 Platinum

Platinum may be used in jewelry (though not often in those intended for pediatric use). It is also used as a chemotherapy agent (i.e., carboplatin, cisplatin, oxaliplatin) for malignant neoplasms, including ovarian, head and neck,

colorectal, and lung. Of these, treatment of low-grade gliomas with platinum-based agents in children has yielded platinum hypersensitivity reactions types I, II, III, and IV [116]. A study by Lafay-Cousin et al. reported that, in children with carboplatin-related hypersensitivity reaction (Cb HSR), the chronology and pattern of symptoms of these hypersensitivity reactions are important to understand [117]. In type I, children present with a transient skin rash and drug fever <38 °C, whereas in type II, urticaria (hives), cough without wheezing, and a drug fever <38 °C are the classic presentation [117]. The presentation drastically changes when carboplatin leads to a type III hypersensitivity reaction, as children will present with face and neck swelling, bronchospasm and wheezing, and serum sickness reaction (arthralgia, lymphadenopathy, joint pain, and myalgia) [117]. Lastly, type IV hypersensitivity reaction leads to respiratory distress, shortness of breath, cyanosis, hypotension, tachycardia, and loss of consciousness [117].

Allergic reactions in 2–30% of children given carboplatin have been reported [118]. Major risk factors include the concentration, frequency, route of administration, and previous exposures. There is also an association with the female gender [116]. Patient hypersensitivity reactions range from mild to severe. In addition, other chemotherapeutic agents that do not contain nickel have been able to initiate an allergic reaction in a previously sensitized individual [96].

37.2.9 Gold

Gold has been reported as a prevalent contact sensitizer in children (5.7%) [119], though the relevance is often uncertain. This has led to the removal of the hapten from comprehensive standard trays globally [119]. That said, it is included on the commercially available patch test kit (T.R.U.E. Test™). Furthermore, experimental studies suggest cross-reactivity with nickel similar to that of copper [94]. Considering copper and gold are in the same column as each other on the periodic table, these metals have the same number of valence electrons, suggesting a potential similar ability to trigger an immunologic response. A positive patch test to gold could theoretically be an adaptive nonspecific response to an underlying nickel sensitization. Both the North American Contact Dermatitis Group (NACDG) data and Mayo Clinic data support a high rate of gold reactivity with unknown relevance in children [120, 121]. Neither study discussed the concordance of the nickel and gold reactions, though the 2001–2004 NACDG data noted both cobalt chloride and gold sodium thiosulfate reactivity of 14.3% in children aged 0–5 years [120]. However, only cobalt, not gold, had a relevant positive patch test in this age group [120]. This nonspecific reactivity in the very young caused gold sodium thiosulfate to be removed from the current 2005–2012 NACDG series and underscores that unless warranted by clinical history, the relevance of testing children with gold is low [120].

Of interest, gold salts are used as treatment in rheumatoid arthritis (RA), as it is hypothesized that macrophages phagocytose the gold and store the metal in lysosomes. Here, gold inhibits antigen processing and subsequently prevents an immune response [122]. However, one study demonstrated that up to 21% of RA patients treated with gold develop a contact allergy [123].

37.2.10 Silver

Silver has not been significantly associated with contact sensitization or ACD in children.

37.3 Patch Test Considerations in Children

Young children may have lowered irritancy thresholds that may be due to inherent differences in the skin barrier and development. Johnke et al. evaluated 562 full-term children at birth, 3, 6, 12, and 18 months of age and found an 8.6% response to nickel utilizing the T.R.U.E Test™ [124]; the majority of which were of unknown relevance. The relevance of this reactivity has not been elucidated. In a follow-up study, children tested pos-

itive for nickel sulfate at 12 and 18 months of age were retested at 3 and 6 years of age. Notably, only 9.5% of those who had previously tested positive for nickel sulfate produced another positive result, suggesting the possibility of false-positive reactivity or change in immune function [125]. Of interest, Schaeffer et al. duplicated testing of 819 children and found that 115 patients were positive on the first patch test, while only 107 were positive on the repeat patch test, and 38 lost their reactivity [126]. Loss of reactivity, or hyporesponsiveness, has been reported in patients with AD and is a reason to support duplicate synchronous testing (clinical observation SEJ).

Alexander Fisher recommended that the allergen concentration for nickel be reduced to half when testing in children under the age of 8 years [127]. Over the age of 6, many practitioners use the same testing substrates and protocols used for adults, and most have removed gold, epoxy, and paraphenylenediamine from routine pediatric patch test trays. Of interest, this is the age at which surface-volume ratio approximates that of the adult and physiologic changes occur that precipitate 60% of children outgrowing atopy between 7 and 12 years of age [128, 129]. In lieu of halving the concentration, the wear time can be reduced to 24 h and/or the allergens may be applied in duplicate (one on the back and one on the inner arm) synchronously. The duplicate increases the immunologic load without increasing the irritancy risk (SEJ practice observation).

37.4 Conclusion

Metals contribute significantly to the prevalence of ACD in children, with Ni-ACD representing the lion's share of reactivity. A complex interplay between inherent barrier function and environmental factors (i.e., staphylococcal colonization and nickel exposure) sets the stage for a dynamic relationship with high morbidity and economic impact, which should not be underestimated. Pediatric patch test specialists play a critical role in the evaluation and management of these afflicted children.

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38 Metal Allergy and Atopic Dermatitis

John McFadden

38.1 Defining Atopic Dermatitis

Atopy is characterised by a predilection for protein allergy, with a T helper (Th) 2 immunological bias, raised IgE and an association with dermatitis, asthma and allergic rhinitis. Atopic dermatitis is characterised by atopy/propensity to protein allergy, a pruritic flexural rash and dry skin with impaired barrier function. There are two commonly used clinical criteria for diagnosing AD and enrolling atopic dermatitis patients into studies [1, 2] (Table 38.1). Both criteria emphasise pruritus, visible flexural rash, dry skin and an association with respiratory disease/allergy. The immunological bias towards Th2 is also supplemented by activation of Th17 and Th22 pathways [3]. An association with filaggrin gene defects has also been recently characterised [4, 5].

38.2 Interpreting Metal Patch Test Reactions in Atopic Dermatitis Patients

False-positive reactions to metals on patch testing, whether follicular, irritant or pustular, are common. This can be particularly accentuated in atopic dermatitis patients [6]. There may be multiple reasons for this. Nickel is an unusual contact allergen in being able to directly bind to toll-like receptors of the innate immune system [7], which is upregulated in atopic dermatitis. As atopic dermatitis is associated with filaggrin functional defects, the binding of nickel to the histidine-rich filaggrin may be impaired, leading to higher irritant doses of nickel entering the skin [8]. One study found that patients with atopic dermatitis had fewer crescendo reactions (strength of patch tests increasing between days 2 and 4) and more strong reactions earlier [9]. A further complication in patch testing to metals, such as nickel in infants whether atopic or not, is that a positive reaction is often not reproducible and can be of questionable relevance [10].

38.3 The Frequency of Metal Allergy in Patients with Atopic Dermatitis

Whilst there are conflicting reports regarding whether metal allergy is more or less common in atopic dermatitis patients, there is general agreement that it is, as in non-atopic dermatitis patients, a significant problem [8, 11, 12]. Before ear piercing, there appeared to be a correlation between atopic dermatitis and nickel allergy, and at one time nickel allergy was even suggested as a minor diagnostic criterion for atopic dermatitis [13, 14]. The severity of atopic dermatitis,

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Table 38.1 Hanifin and Rajka's criteria and the UK working party's diagnostic criteria for atopic dermatitis

Hanifin and Rajka criteria for atopic dermatitis	
Major criteria(must have three)	• Pruritus • Dermatitis affecting flexural surfaces in adults or face and extensor surfaces in infants • Chronic or relapsing dermatitis • Personal or family history of cutaneous or respiratory allergy
Minor criteria (must have three)	• Facial features o Facial pallor, erythema, hypopigmented patches, infraorbital darkening, cheilitis, infraorbital folds, recurrent conjunctivitis, anterior neck folds • Triggers o Emotional factors, environmental factors, food, skin irritants • Complications o Susceptibility to skin infections, impaired cell-mediated immunity, predisposition to keratoconus and anterior subcapsular cataracts, immediate skin reactivity • Other o Early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris, hand and foot dermatitis, nipple eczema, white dermatographism, perifollicular accentuation
UK working party diagnostic criteria for atopic eczema	
Itchy skin condition (required)	
Three of the following	• Visible flexural eczema, e.g. antecubital and popliteal fossae (or visible dermatitis of the cheeks and extensor surfaces if under 18 months) • Personal history of dermatitis as above • Personal history of dry skin in the last 12 months • Personal history of asthma or allergic rhinitis (or history of eczema in a first-degree relative if <4 years old) • Onset of signs and symptoms under the age of 2 years (this criteria should not be used in children <4 years)

whether the atopic dermatitis is current or past and whether atopic dermatitis is extrinsic or intrinsic in nature, may also have an influence. Herro et al. [11] studied the frequency of contact allergy in patients with atopic dermatitis compared to controls. They found a non-statistically significant higher frequency amongst atopic dermatitis patients of nickel (35% vs 26%), cobalt (13% vs 4%) and chromium (11% vs 4%) allergy. However, the numbers involved were small (n = 101). Giordano-Labadie et al. [15] also found a high frequency amongst children with atopic dermatitis (n = 137) of allergy to nickel (15%) and less so to chromium (N = 2.6%) and cobalt (N = 1.7%). In contrast, Thyssen et al. [8] found that patients with severe atopic dermatitis and asthma have an overall lower prevalence of contact sensitisation, whereas mild-to-moderate disease did not suppress contact sensitisation. Allergy rates amongst atopic dermatitis patients in comparison to all patients (n = 15,461), respectively, were 9.69% vs 12.6% to nickel, 3.94% vs 3.8% to cobalt and 3.28% vs 2.6% to chromium. Amongst 989 patients, McFadden and Cronin [16] found a trend towards higher nickel allergy amongst patients with historical atopic dermatitis (23.2%) compared to patients with current atopic eczema (18.3%) and patients without atopic eczema (18.2%).

Whereas extrinsic atopic dermatitis is characterised by impaired skin barrier, high IgE and a Th2 preponderance, intrinsic AD is not associated with impaired skin barrier and has normal IgE levels and, in comparison to extrinsic AD, a preponderance towards Th1 [17]. Yamaguchi et al. [17, 18] found high frequencies of positive nickel/cobalt patch tests in patients with intrinsic AD. Intrinsic AD patients showed significantly higher percentages of positive reactions to nickel (intrinsic 41.9% vs extrinsic 16.4% p = 0.019) and cobalt (38.7% vs 10.9% p = 0.005). Furthermore, they found higher levels of nickel in the sweat of intrinsic AD patients as compared to extrinsic AD

patients (333.8 vs 89.4 ng/g $p = 0.0005$), which inversely correlated with IgE. They also found that serum nickel levels were significantly higher in intrinsic versus extrinsic AD patients.

A recent large general population study from Europe found no difference in nickel allergy rates between atopic dermatitis patients and the rest of the general population [19]. Collectively, data are conflicting; however, it is likely that the risk of nickel allergy is increased in individuals with mild atopic dermatitis but that the common practice of ear piercing has obscured this association.

38.4 Immunological and Skin Barrier Considerations in Atopic Dermatitis

38.4.1 In Atopic Dermatitis Patients, Contact Allergy Pathways Occur Through the Th2 System

Allergic contact dermatitis is predominately a Th1-driven immune response, whereas atopic dermatitis is Th2 driven. Newell et al. [20] studied the immune pathways regarding contact sensitisation in atopic dermatitis patients and non-atopic individuals. They demonstrated:

a. Equal penetration of the contact allergen 2,4-dinitrochlorobenzene (DNCB) in uninvolved atopic dermatitis skin versus a normal individual's skin.
b. Experimental contact sensitisation responses were reduced in atopic dermatitis individuals.
c. Although both showed Th1 responses, this was reduced in atopic dermatitis individuals and was associated with significantly reduced contact allergen-specific Th2 responses.

There are, therefore, fundamental differences in allergic contact dermatitis mechanisms between those with atopic dermatitis and normal individuals.

38.4.2 Changes in the Innate Immunity in Atopic Dermatitis May Influence the Response to Metal Contact Allergens

Kim et al. [21] have summarised these as:

a. Reductions in level and functionality of antimicrobial peptides
b. Suppression of toll-like receptor function by Th2 cytokines
c. Increased expression of thymic stromal lymphopoietin (TSLP), which is involved in the activation of Langerhans and dendritic cells to induce Th2 immune responses

These may be of particular relevance to metal allergens, which appear to have the ability to stimulate toll-like receptors through histidine binding and do not require production of reactive oxidative species to induce danger signals in order to stimulate the innate immune system [22].

38.4.3 Bacterial Colonisation of Atopic Dermatitis Could Enhance Sensitisation to Metal

The atopic dermatitis skin is readily colonised by *Staphylococcus aureus*. This may theoretically enhance sensitisation to metal:

a. The presence of bacterial lipopolysaccharide may enhance the immune signalling triggered by contact allergens [12].
b. Staphylococcal enterotoxin B is a superantigen which triggers expansion of the Vbeta 17 subgroup of T lymphocytes. This subgroup is also expanded in the clonal expansion of nickel-reactive T cells [12].
c. It has also been reported that metal contact sensitivity to agents contained within orthopaedic prostheses is twice as likely in the presence of bacterial infection [23].

d. Staphylococcal superantigens promote the production of cytokines such as IL-1 and TNF-alpha which are involved in contact sensitisation [24].

38.4.4 Filaggrin Gene Mutations Associated with Atopic Dermatitis May Affect Penetration of Metal Allergens

The skin in atopic dermatitis is characterised by xerosis as a result of either a genetic predisposition or of inflammation following exposure to exogenous stressor agents [12]. Mutations in the filaggrin gene are associated with reduced skin hydration and increased transepidermal water loss and skin pH. Th2 inflammation also reduces the expression of filaggrin molecules, leading to an acquired filaggrin deficiency [25, 26]. A positive association between filaggrin gene mutations and both metal dermatitis and contact sensitivity to nickel was found amongst German adults and amongst Danish adults without ear piercings [12]. The filaggrin molecule is rich in histidine, which can bind nickel, and a deficiency may therefore allow a greater penetration of nickel ions through the skin barrier ([12, 27, 28]). Chromium is another metal allergen that may also more readily penetrate the filaggrin-deficient skin [29].

38.5 Clinical Considerations

38.5.1 Unusual Sources of Nickel Exposure

Classic allergic contact dermatitis to metals may often present as a reaction to nickel and cobalt in jewellery, e.g. ear dermatitis from earrings or neck dermatitis from a necklace or from metal in clothing, e.g. the button on a pair of jeans resulting in a round dermatitis on the abdomen. Allergic contact dermatitis from chromium may classically occur on the hands from wet cement exposure or on the feet from leather. However, one must remain aware of unusual presentations of allergic contact dermatitis and newer sources of metal exposure, especially in younger patients. Aquino et al. [30], for example, found that 90% of flip phones tested positive for nickel—this should be kept in mind when seeing patients with unusual or asymmetrical dermatitis on the face and/or hands. Similarly, laptops are a potential source of nickel allergy, with hand, lap or widespread dermatitis having been reported [31]. Dermatitis on the bridge of the nose, below the eyes, linearly on the cheeks or in the retroauricular area may come from nickel in eyeglass frames. A round rash on the posterior aspect of the thigh in a schoolgirl was reported to be caused by allergic contact dermatitis to nickel from a metal bolt exposed on the seat of a school chair [32].

38.5.2 Irritant Contact Dermatitis to Metal in Atopic Dermatitis Patients

Möller and Svensson [33] found that a high percentage of patients with atopic dermatitis had a strong history suggestive of nickel allergy but negative patch tests. They suggested this as one criterion for detecting atopy. Another interpretation is that irritant reactions from metal objects may be more prominent in atopic dermatitis individuals due to such factors as impaired skin barrier function, accounting for a positive history for reacting to metals but a negative patch test.

38.5.3 Are Atopic Dermatitis Patients More Prone to Secondary Spread from the Original Site of Allergic Contact Dermatitis?

A characteristic of allergic contact dermatitis is its potential to spread away from the site of original exposure, e.g. an id reaction. This was described by Calnan and Wells [34], reporting on allergic contact dermatitis to nickel in suspenders. He described the secondary sites as being

unrelated to the area of the primary site of nickel contact (in this case, the thigh). Three out of four of his patients developed secondary spread, principally on the elbow flexures, eyelids, inner thighs and also of a generalised nature. The areas of secondary spread were, therefore, often flexural in nature. However, Calnan's cohort had a low prevalence of atopic disease.

Could atopic dermatitis patients be less 'efficient' at containing allergic contact dermatitis and more prone to 'secondary spread'? The analogous pathways in the immune response to microbial infection and allergic contact dermatitis have been recently highlighted by several authors [35, 36]. Patients with atopic dermatitis appear to be less 'efficient' at containing local skin infections, with subsequent dissemination. Several reports observe that molluscum contagiosum infections in atopic dermatitis are more disseminated, with atopic eczema also often appearing around the disseminated papules [37–39]. Atopic dermatitis patients are similarly more prone to disseminated infections with herpes simplex and staphylococcus [40, 41]. There appears to be a 'positive loop' effect in many of these reports, with the atopic dermatitis allowing dissemination of the infection and also the disseminated infection encouraging spread of the atopic dermatitis.

Schena et al. [42] looked at over 300 children with allergic contact dermatitis; approximately a third of these also had atopic dermatitis. They noted that the atopic dermatitis group was more likely to have more generalised dermatitis. Tamagawa-Mineoka et al. [43] found that a significant number of patients (15/45) with widespread, recalcitrant atopic dermatitis had contact allergy (nickel being the most common), and avoidance of the allergen greatly or partially improved the dermatitis in 9/15 of these patients.

Williams et al. [44] described six patients with previous childhood atopic dermatitis, now quiescent, who entered manual work with exposure to contact allergens and irritants. They developed hand eczema with subsequent spread to flexural areas in keeping with an atopic dermatitis. The authors questioned whether this was re-exacerbation of atopic dermatitis or auto-eczematisation with secondary spread, as originally described by Calnan and Wells [34]. They noted that the dermatitis patterns of both may be indistinguishable. The phenomenon of an apparent flare of quiescent atopic dermatitis following exposure to contact allergens and/or irritants has subsequently been termed 'chemical atopy' [42]. It is tempting to speculate that the typical flexural pattern seen in atopic dermatitis and the 'autoeczematisation' seen in Williams' cohort and in 'chemical atopy' are pathophysiologically indistinguishable and both a manifestation of a Th2-skewed cutaneous immune system's inability to efficiently control eczematous inflammation.

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Metal Allergy in Asia

39

Anthony Goon

39.1 Introduction

Metals dominate the top ten most common contact allergen lists in most patch test centres worldwide. Nickel, chromium and cobalt often occupy positions in the top five whenever standard series results are published. This is also true in most of Asia. Tables 39.1 and 39.2 show the common metal allergens causing contact allergy in various patch test centres in Asia over the years and their rankings within the top ten allergens in the standard series of their respective populations. Table 39.1 includes studies of patients tested with the standard series of the various centres [1–19], while Table 39.2 shows studies focusing only on metal allergy, and hence their results are not directly comparable with those of the populations in Table 39.1 [20–22].

Additionally, gold had been recently quoted as the most common source of metal sensitivity in Thailand [1]. Mercury and palladium also had prominent places as common causes of contact dermatitis among dental workers in South Korea [23]. In the past, reports of gold dermatitis caused by ear piercing [24, 25] and baboon syndrome caused by mercury from broken thermometers [26, 27] had been relatively more common in Japan.

The epidemiology of metal allergy in Asia on the whole is similar to that of the rest of the world. Costume jewellery, ear piercing, cement, leather, dental materials and metal instruments have been implicated as common sources of sensitisation. Rarer causes quoted included desert dust, canned food and seafood ingestion, joint prostheses and coronary stents.

39.2 Patterns of Metal Allergic Contact Dermatitis Peculiar to Asia

39.2.1 Scarf Brooch

Allergic contact dermatitis from nickel is not typically seen on the anterior neck in most parts of the world including the Middle East, but it had once been fashionable for Muslim women in Malaysia and Singapore to use metal scarf brooches to fasten their scarves, leading to direct contact of nickel-releasing metal with the skin and resultant allergic contact dermatitis (Fig. 39.1).

39.2.2 Desert Dust

Reports of skin allergic reactions to desert dust have been made in Japan. Atmospheric pollutants, which include heavy metal dust, are regularly displaced to the Japanese archipelago by dust storms originating

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Table 39.1 Rankings in frequency of patch test positivity of nickel, chromium, cobalt, and other metal allergens in Asian patch test centres. Data from case series analyzing entire standard series of these centres

Authors	Population tested	Year(s) of testing	Centre(s)	Nickel	Chromium	Cobalt	Others
Boonchai and Iamtharachai	852 to "Siriraj standard series"	2000–2009	Bangkok	2nd	3rd	5th	Gold 1st
Boonchai et al.	323 to extended European standard series	2004–2006	Bangkok	2nd	1st	4th	
Rohna et al.	346 to European standard series	1994–1996	Kuala Lumpur	1st	8th	5th	
Goh CL	2471 to ICDRG standard battery	1984–1985	Singapore	1st	3rd	6th	
Lim et al.	5557 to modified European standard series	1986–1990	Singapore	1st	9th	7th	
Unpublished	5819 to modified European standard series	1992–1996	Singapore	1st	8th	4th	
Tee et al.	3277 to modified European standard series	2004–2008	Singapore	1st	3rd	Not in std. series	
Ochi et al.	2598 to modified European standard series	2009–2013	Singapore	1st	4th	Not in std. series	
Lam et al.	2585 to European standard series	1995–1999	Hong Kong	1st	9th	3rd	
Lee and lam	490 to European standard series	1987–1988	Hong Kong	2nd	>10th	3rd	
Lee and lam	231 to European standard series	1986	Hong Kong	2nd	6th	3rd	
Wang et al.	88 to European standard series	1992–1993	Shanghai	1st	2nd	4th	
Li et al.	217 to modified European standard series	2001–2002	Beijing	1st	5th	Not in std. series	
Zhang et al.	124 to European standard series	1989	Beijing	2nd	1st	3rd	
Kim et al.	715 to Korean standard series	2005–2012	Seoul	1st	3rd	2nd	
Akasya-Hillenbrand and Ozkaya-Bayazit	542 to extended European standard series	1996–1999	Istanbul	1st	2nd	4th	Palladium 3rd
El-Rab and al-sheikh	240 to European standard series	Not mentioned	Riyadh	1st	2nd	3rd	

Table 39.1 (continued)

Authors	Population tested	Year(s) of testing	Centre(s)	Nickel	Chromium	Cobalt	Others
Sharma et al.	220 to Indian standard series	Not mentioned	New Delhi	1st	3rd	4th	
Sharma and Chakrabarti	200 to European standard series	Not mentioned	Chandigarh	2nd	1st	4th	
Shenoi et al.	212 to extended European standard series	1992–1993	Manipal	3rd	2nd	6th	

Table 39.2 Rankings in frequency of patch test positivity of nickel, chromium, cobalt, and other metal allergens in Asian patch test centres. Data from case series focusing specifically on metal allergens

Authors	Population tested	Year(s) of testing	Centre(s)	Nickel	Chromium	Cobalt	Others
Goon et al.	3047 to modified European standard series	2001–2003	Singapore	1st	3rd	2nd	Gold 4th
Cheng et al.	3559 to European standard series	1978–2003	Taipei	1st	3rd	2nd	Copper 4th
Nonaka et al.	931 to metal series	1990–2009	Tokyo	1st	5th	3rd	Mercury 2nd, palladium 4th

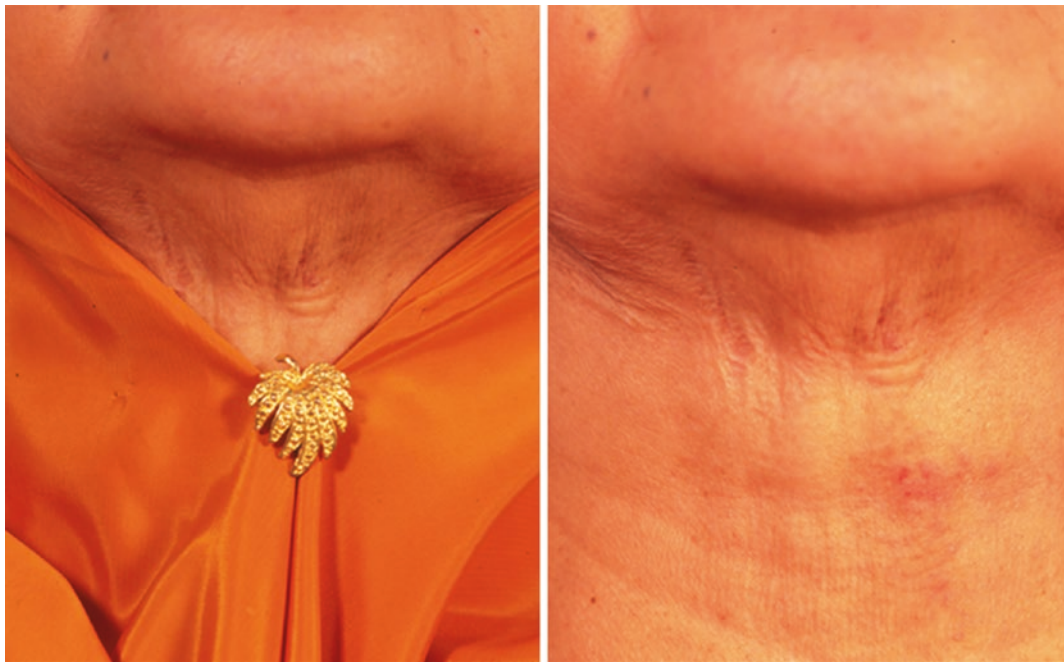

Fig. 39.1 Allergic contact dermatitis from nickel in a scarf brooch

from the Chinese and Mongolian deserts. Particulate matter in the dust comprises rock-forming minerals as well as clay minerals. Common minerals include quartz, feldspar, mica, kaolinite and chlorite. Analysis of dust particles revealed the presence of heavy metal compounds that are not thought to originate from the soil; rather, these compounds probably originated from man-made pollutants adsorbed from the atmosphere in transit [28].

Patients with exposure to Asian dust were divided into those with and those without skin symptoms and patch tested to $ZnCl_2$ 2%, $MnCl_2$ 2%, $Cr_2(SO_4)_3$ 2%, $FeCl_3$ 2%, $AlCl_3$ 2%, $NiSO_4$ 5% and Asian dust particles. Although not mentioned in the article itself, it is presumed that the vehicle was petrolatum. Positive reactions to ferric chloride, aluminium chloride, nickel sulphate and Asian dust particles were more common in those with skin symptoms than those without. The authors of the article concluded that the skin symptoms may have been allergic reactions to metals bound to Asian dust particles [29].

39.2.3 Pewter

Anecdotal reports of airborne exposure dermatitis from pewter dust in Malaysia have been mentioned in passing, where patients had been patch tested to pewter dust brought from the patients' workplace [30, 31]. However, there have not been any well-documented cases or case series with confirmed diagnoses of pewter contact dermatitis in the available peer-reviewed literature.

39.3 Mucocutaneous Reactions from Metals Due to Non-cutaneous Exposure

Contact dermatitis and other skin reactions from metal allergens due to non-skin exposure have been reported in several Asian centres. The majority were from Japan, where there have been reports of oral lichen planus [32], palmoplantar pustulosis [33] and systemic contact dermatitis [34, 35] from zinc in dental fillings and other dental restorations. A case of occupational systemic contact dermatitis from cobalt likely due to cobalt inhalation [36] in a patient who had worked as a grinder in a hard metal factory was reported in Japan.

39.4 Metal Allergy from Medical Devices and Oral Supplements

In Japan, nickel allergy has been implicated as a major factor in chronic refractory in-stent restenosis in patients with bare-metal coronary stent implants [37]. An extremely rare case of systemic contact dermatitis caused by exposure to chromium after a total knee arthroplasty has been reported in China [38]. Systemic contact dermatitis after ingestion of chromium chloride in a multivitamin/multimineral tablet has been reported in Turkey [39].

39.5 Nickel Allergy from Underground Water

A Korean woman was reported to have recurrent contact dermatitis of the face due to nickel in underground water [40]. She had been using underground water instead of domestic tap water at home for 3 years.

39.6 Conclusion

In a study of ten European patch test centres from 2005 to 2006 [41], the prevalences of nickel, cobalt and chromium allergies had been quoted as 19.7–24.5, 6.2–8.8 and 2.4–5.9%, respectively. The data from the articles in Table 1 of this chapter, for which percentages had been quoted or could be inferred, showed a very wide variability: nickel 10.8–27.6%, cobalt 3.7–23.5% and chromium 1.5–29%.

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Part VII

Uncommon Manifestations of Metal Allergy

Metal Allergy and Contact Urticaria

40

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40.1 Introduction

Although an abundance of different metals exists, most humans are only exposed to a minority of these, and only some cause sensitization. As opposed to delayed type IV hypersensitivity reactions to metals, which are well documented [1], cutaneous type I hypersensitivity reactions are rarely reported. In this chapter, we briefly describe clinical and epidemiological features of contact urticaria and review the existing literature on contact urticaria caused by metals.

40.2 Contact Urticaria

Contact urticaria is defined by a cutaneous wheal and flare reaction after external contact with an eliciting agent. The reaction usually appears within minutes and clears completely within hours leaving no residual signs of inflammation or scarring [2].

Contact urticaria can be classified as either non-immunological (irritant) or immunological (allergic), according to the underlying mechanism. Immunological contact urticaria results from a type I hypersensitivity reaction mediated by pre-formed IgE antibodies and mast cells. In contrast, non-immunologic contact urticaria is not IgE mediated; however, the exact pathogenesis of this disease entity is not fully understood. For some of the classic urticariogens, such as dimethyl sulfoxide, induction of mast cell degranulation and release of epidermal prostaglandins are believed to be caused by local blood vessel damage at the site of contact [3]. However, each trigger substance presumably has its own mechanism of action.

Clinical manifestations of immunological contact urticaria have the potential to extend beyond the point of contact with the noxious agent. Generalized urticaria, along with involvement of respiratory and gastrointestinal organs, may develop with the potential to culminate in anaphylactic shock (Table 40.1) [3]. This potential for multisystem involvement led to the definition of the term contact urticaria syndrome, introduced

Table 40.1 Diseases involved in the contact urticaria syndrome (Reproduced with permission from [3])

Stage 1	Contact urticaria Immediate contact dermatitis Nonspecific symptoms (itching, tingling, burning sensation)
Stage 2	Generalized urticaria
Stage 3	Bronchial asthma Rhino-conjunctivitis Orolaryngeal symptoms Gastrointestinal dysfunction
Stage 4	Anaphylaxis Anaphylactoid reaction

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by Maibach and Johnson in 1975 [4]. Figure 40.1 summarizes a proposed algorithm for diagnosing immediate contact hypersensitivity reactions, including contact urticaria suspected to be caused by metals. Life-threatening anaphylactic reactions have been reported during diagnostic skin testing with metals [5, 6] and, in general, testing should only be performed if resuscitation equipment and trained personnel are readily available.

Epidemiological data regarding contact urticaria are sparse. A frequency of 1–3% is reported in the general population, while the prevalence in healthcare workers in Europe varies from 5 to 10% [3]. In Australian data, 8.3% of patients with occupational skin disease suffered from contact urticaria, mainly due to latex, food sources, and ammonium persulfate [7]. A typical wheal and flare reaction is easily diagnosed by the clinician, but the reaction after exposure to diluted classical urticariogens can be limited to erythema or even pruritus as the only evident symptom [8], thereby making diagnostics more difficult. Hence some degree of underdiagnosing is believed to occur, especially regarding non-immunological contact urticaria.

40.3 Contact Urticaria and Nickel

Nickel belongs to the group of transitional metals. With its widespread use in products such as alloys, coins, cosmetics, jewelry, orthopedic implants, and household utensils, skin exposure is common both in an occupational and nonoccupational setting. Although nickel is a frequent and well-established cause of delayed type IV hypersensitivity, nickel-induced type I hypersensitivity eliciting an urticarial response has rarely been reported. The mechanism behind the immediate contact inflammatory reactions to nickel is not fully understood.

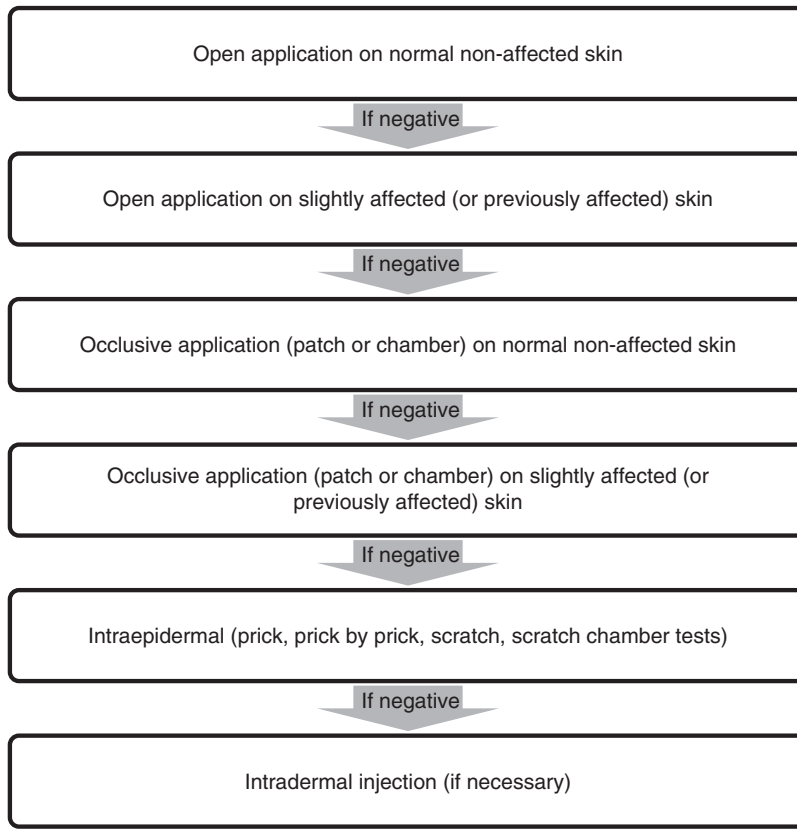

Fig. 40.1 Proposed algorithm for the diagnosis of immediate skin contact reactions (Reproduced with permission from [3])

Initially, it was thought that nickel may act as a mast cell discharger on a non-immunological basis [9]. In one of the more recently published case reports discussed below, a positive radioallergosorbent test (RAST) indicated that the observed urticarial reaction to nickel was, at least partly, IgE mediated [10]. Nevertheless, the reported case was the only patient in a 15-year period with a positive RAST to nickel among nickel allergic patients at this facility, and the absolute titer was relatively low. The frequency of contact urticaria caused by nickel in the general population is unknown. In a recent study of 69 patients with positive patch tests to nickel, 24.6% had a history of urticarial symptoms [11]. The few published cases on contact urticaria caused by nickel include individuals with both occupational and nonoccupational exposure (see Table 40.2).

Osmundsen [12] was the first to report two cases of contact urticaria caused by nickel exposure. The first patient, a 30-year-old female cleaner, experienced immediate itching and burning of her palms and fingertips followed shortly after by erythema and edema when handling a bucket with a metal handle. Standard patch testing with nickel showed a ++ reaction, while

Table 40.2 Case reports on contact urticaria caused by nickel

Author	Patient(s)	Exposures	Diagnostic tests	Results
Osmundsen (1980) [12]	30 yo female	Metal handle on plastic bucket	Both patients: 20-min patch test $NiSO_4$ 2.5% CPT $NiSO_4$ 2.5%	Both patients: 20-min patch test on normal skin negative. CPT positive for urticaria after 20 min
	19 yo female	Jewelry		
Malo (1982) [13]	28 yo male	Metal plating factory worker	SPT $NiSO_4$ 1%	SPT positive
Tosti (1986) [14]	24 yo female	Surgical tools, jewelry	SPT $NiSO_4$ 1% Standard patch test $NiSO_4$ 2.5% Open patch test $NiSO_4$ 5%	SPT positive after 3 min Patch test positive Open patch test positive after 24 h
Valsecchi (1987) [15]	59 yo female	Jewelry	Standard patch test $NiSO_4$ 30 min patch test $NiSO_4$ 5%	Standard patch test positive (+++) 30-min patch test positive for urticaria
Estlander (1993) [10]	27 yo female	Manual grinding of metal casts, jewelry	Standard patch test $NiSO_4$ 2.5% SPT $NiSO_4$ 0.1% and 1% Scratch chamber test $NiSO_4$ 0.1% and 1% 1-h open test $NiSO_4$ 1% Specific IgE (RAST) for $NiSO_4$	Standard patch test positive SPT 1% and scratch chamber test 1% both positive for urticaria 1-h open test positive for urticaria Increased specific IgE for $NiSO_4$
Helgesen (1997) [26]	19 yo female	Coins, doorknobs, bannisters	SPT $NiSO_4$ 2.5% Patch test (open and closed) $NiSO_4$ 0.01%, 0.1%, and 1% Aluminum Finn® chamber Aluminum powder in pet	SPT $NiSO_4$ 2.5% positive Open patch test positive on arm at 10 min to $NiSO_4$ 0.1% and 1%, negative on back Closed patch test positive on arm and back after 1 h and 2 h to $NiSO_4$ 0.1% and 1% Aluminum chamber positive at 2 h on arm and back Aluminum powder positive at 1 h on arm and back
Walsh (2010) [16]	38 yo female	Dental procedures and cutlery	20 min patch test $NiSO_4$ 1%, 3%, and 5%	All patch tests positive for urticaria after 20 min

CPT chamber prick test, *SPT* skin prick test, *yo* year-old

20-min patch testing with 2.5% nickel sulfate on normal skin of the forearm was negative. A chamber prick test with 2.5% nickel sulfate elicited a strong urticarial reaction after 20 min. A dimethylglyoxime test of the metal handle was strongly positive for nickel.

The second patient, a 19-year-old female, experienced immediate swelling and redness of her earlobes after applying ear clips. Similarly to the first patient, a 20-min patch test with 2.5% nickel sulfate on normal skin was negative, while a positive chamber prick test was observed. The patient tested negative to standard patch testing with nickel. As negative controls, five patients with a positive 48-h patch test to nickel and three patients with chronic urticaria were tested with chamber prick test with nickel sulfate 2.5%. No immediate reactions were observed.

Malo et al. [13] described a 28-year-old man working at a metal plating factory. A year after nickel sulfate was introduced in the electroplating process at the facility, the patient developed an urticarial rash on his arms and legs. The rash was only present when the patient was at work and cleared within a few hours after leaving work. Later, the patient also developed asthmatic symptoms. Skin prick testing with 1% nickel sulfate gave a positive reaction, while eight control subjects showed no positive reactions. When the patient was tested with a specific inhalation challenge with nickel sulfate, he developed a bronchial response suggestive of asthma.

Tosti et al. [14] described a 24-year-old woman who at 13 years of age, following an appendectomy, developed an urticarial reaction and postoperative peritonitis. She had previously noticed immediate redness and swelling after contact with jewelry. As no evidence of antibiotic hypersensitivity existed, it was suspected that other hypersensitivity reactions could possibly explain the observed postoperative complications. A skin prick test with 1% nickel sulfate was positive after 3 min. A standard patch test also showed a positive ++ reaction to nickel, and an open patch test with 5% nickel sulfate gave a positive reaction after 24 h. The authors mentioned nickel-plated cannulas as a possible relevant exposure; however, no further testing was reported.

In another case report, Valsecchi and Cainelli [15] describe a 59-year-old woman, who had been suffering from unspecified lesions on the hands and ears for 6 months. The lesions on the hands changed during the day. She claimed that the lesions on her ears and left wrist were caused by contact with jewelry. The patient was patch tested with standard contact allergens and had a positive +++ reaction to nickel sulfate at 48 and 96 h. A 30-min patch test with 5% nickel sulfate on the forearm gave a strong urticarial reaction mimicking the reaction described by the patient.

Estlander et al. [10] described a 27-year-old woman suffering from nickel-induced allergic contact dermatitis. After working with manual grinding of metal casts for 2 years, she developed symptoms of contact urticaria, rhinitis, and asthma at work. The symptoms cleared completely during weekends and holidays. Standard patch testing showed a positive reaction to 2.5% nickel sulfate. The patient also had positive reactions to a skin prick test and a scratch chamber test with 1% nickel sulfate. An open patch test with the same nickel solution elicited an urticarial reaction on the volar forearm after 45 min. Specific IgE for nickel was evaluated by RAST and was slightly elevated. The patient had a nasal provocation test and a specific inhalation challenge performed with nickel sulfate, and a nasal and bronchial response was elicited within minutes.

In 2010, Walsh et al. [16] described a 38-year-old atopic woman with a history of reacting to dental procedures since childhood. Immediately after exposure to dental instruments, she would develop pain and oral swelling. She also suffered from immediate pain and pruritus of the palms, followed by swelling and erythema within an hour after contact with cutlery. Furthermore, the patient had experienced immediate urticarial symptoms during venesection. When patch tested with nickel sulfate at 1%, 3%, and 5% concentrations on the volar side of the forearm, the patient immediately complained of discomfort under the chamber containing the 5% solution and

developed an urticarial reaction after 20 min at all three test sites.

40.4 Contact Urticaria and Chromium

The French chemist Louis Nicolas Vauquelin discovered chromium in 1797. Chromium, belonging to the group of transitional metals, is among the most commonly found metals in the Earth's crust and has found wide applications in areas such as electroplating processes, metal alloys, tanning of leather, cement, paint, and production of chromate salts. Chromium metal is non-allergenic; however, several chromium salts can cause irritation and allergic contact dermatitis [17]. Previously, occupational exposure to chromium in cement was a common cause of contact allergy due to a high content of hexavalent chromium. International regulations of the allowed content of hexavalent chromium in cement have changed the epidemiology of chromium sensitization within European nations. Today, leather products are responsible for the main exposure to chromium [18], where it is estimated that up to 90% of leather produced globally is tanned using chromium [19].

Although chromate is a common cause of delayed hypersensitivity and allergic contact dermatitis, the literature on contact urticaria caused by exposure to chromate is sparse. In 1993, Pizzino [20] described a case of possible contact urticaria caused by exposure to chromate in a 26-year-old man working at a facility producing pipes that were electroplated with chromate. The patient would hose down pipes that had been in open baths containing chromic and sulfuric acids resulting in a mixture of water and chemicals splashing onto his skin. His protective equipment consisted of a cloth apron and respirator. The patient initially developed eczema on his hands and arms, followed by an urticarial rash on most of the body including his face. The urticaria persisted for more than 1 year, where the patient was still exposed to chromate at work. Initial diagnostic workup of the patient showed a positive standard patch test to chromate (++). The patient was further extensively evaluated for other causes of chronic urticaria, but his lesions did not resolve until several months after he was completely withdrawn from occupational chromate exposure.

40.5 Contact Urticaria and Cobalt

Cobalt is a hard, silver-gray metal belonging to the group of transitional metals. Cobalt is mainly a by-product from nickel and copper mining. Cobalt is utilized in the production of hard metal alloys, diamond tooling, dyes (blue pigment), magnets, and electronics [21]. Contact allergy to cobalt chloride is common, often associated with concomitant patch test reactivity to nickel or chromate. The frequency of cutaneous type I hypersensitivity to cobalt is unknown, and only a few case reports have been published [6, 22, 23], including a case of anaphylaxis [6]. It has been suggested that cobalt chloride causes contact urticaria through a non-immunological mechanism by inducing the release of vasoactive amines from mast cells [22].

Smith et al. [22] described a 20-year-old man, suffering from X-linked ichthyosis, who experienced contact urticaria following a provocative sweat test. The patient was painted with a mixture of cobalt chloride 10% dissolved in 95% isopropyl alcohol as a color indicator on the neck, arms, trunk, and legs. Seconds after application, the patient noted a stinging sensation in the painted areas, and after 5 min, urticaria developed in the involved areas above the waist. As part of the diagnostic workup to further study the urticaria-producing effect of cobalt chloride, 36 control subjects were tested. A 9-year-old girl developed similar urticarial lesions within minutes after application of the cobalt chloride solution, with the reaction subsiding within 30 min. No skin prick tests or patch test results were reported.

Krecisz et al. [6] reported a 39-year-old nonatopic woman employed as a ceramics decorator. After 3 months of work, the patient developed eczema on the back of her hands and forearms. Subsequently, after continuing work for 5 years,

the patient also developed generalized urticaria, with facial angioedema and general fatigue after working with a blue paint containing cobalt chloride. As the patient was transferred to a different work area, her symptoms disappeared, and she did not have a diagnostic workup performed until 2 years later. Standard patch testing revealed contact allergy (+++) to both nickel sulfate and cobalt chloride. A skin prick test was positive for cobalt chloride (0.1 and 1 mg/mL) only, and cobalt-specific IgE was elevated at 2.97 IU/mL. The patient had a challenge test performed, in which she painted pottery using the blue cobalt-containing paint from her previous workplace. After 30 min, the patient developed urticarial lesions on her hands and forearms, followed by facial angioedema, and the test was regarded positive. Although the exposure was stopped, the patient developed an anaphylactic reaction with hypotension and tachycardia and was successfully treated with intravenous corticosteroids.

Bagnato et al. [23] described a case of contact urticaria to cobalt in a 42-year-old man following a blue-colored tattoo. However, the patient did not develop any urticarial symptoms until 2 months after the tattoo was made, and no test to diagnose immediate cutaneous hypersensitivity was reported.

40.6 Contact Urticaria and Aluminum

Aluminum and its salts are rarely reported to cause contact allergy, especially considering the common and widespread exposure in various consumer products including antiperspirants and sunscreens along with medical preparations. However, the diagnosis of type IV hypersensitivity to aluminum is complicated with regard to choosing the optimal aluminum test compound and concentration [24]. Recent attention on cutaneous reactions to aluminum has focused on type IV allergic reactions in relation to administration of injectable vaccines where aluminum salts are used as adjuvants. Up to 1% of children develop vaccination granulomas following injection of aluminum-adsorbed vaccines, and of these, 77–95% develop contact allergy to aluminum [25]. The frequency of cutaneous type I hypersensitivity reactions to aluminum is unknown.

Helgesen and Austad described the only case of contact urticaria to aluminum [26]. A 19-year-old woman reported experiencing a burning sensation and pain within minutes after contact with metal objects such as coins, doorknobs, and bannisters. Shortly after, vesicles and bullae would appear, developing into ulcerations and erosions on the subsequent day. The patient had a positive skin prick test to nickel sulfate and an immediate urticarial reaction to both open and closed patch tests with nickel on the forearm. When tested with an empty aluminum Finn® chamber, erythema and infiltration appeared after 2 h. Applying pure aluminum powder in petrolatum to the skin resulted in an immediate inflammatory reaction after 1 h.

40.7 Platinum Group Elements

The platinum group elements (PGEs) include the metals platinum, iridium, palladium, rhodium, ruthenium, and osmium. Unique properties including high melting points, corrosion resistance, and catalytic qualities make PGEs valuable in many industries. All PGEs are rare elements of the Earth's crust. Delayed contact hypersensitivity to PGEs is presumably not as common as type I hypersensitivity, especially in an occupational setting: In a catalyst production facility where 153 workers were evaluated for contact hypersensitivity to PGEs, two workers (1.3%) had an urticarial reaction 25 min after skin prick testing with hexachloroplatinic acid, which was similar to the frequency of type IV hypersensitivity to PGE salts among the workers. In total, 14.4% of the workers had a positive skin prick test to any of the PGE salts tested with concentrations ranging from 10^{-8} to 10^{-2} mol/L. Rhinitis and asthma were the clinical symptoms reported most often in patients with a positive skin prick test [27, 28].

40.7.1 Contact Urticaria and Platinum

Platinum is a highly reactive transitional metal which easily complexes with donor groups in amino acids to form a complete antigen [29]. The platinum compounds eliciting hypersensitivity are confined to a small group of ionic complexes containing reactive halogen ligands. IgE antibodies to platinum salts have previously been demonstrated in sensitized workers [30]. Chlorinated soluble compounds such as hexachloroplatinic acid ($H_2[PtCl_6]$) and its potassium and ammonium salts, along with potassium and sodium tetrachloroplatinate ($K_2[PtCl_4]$, $Na_2[PtCl_6]$), represent the most dangerous chemical forms [27]. Platinum is used in catalytic converters, laboratory equipment, electrical contacts and electrodes, platinum resistance thermometers, dentistry equipment, and jewelry. Chemotherapeutic compounds containing platinum, such as carboplatin and cisplatin, are applied in the treatment of certain cancer types. Between 12 and 24% of patients receiving oxaliplatin have been reported to develop an immediate hypersensitivity reaction to the drug after multiple intravenous injections [31].

Schena et al. [32] described a 35-year-old nurse, who after 6 months of working in an oncological department developed urticarial lesions on the face, chest, arms, and dorsa of the feet 30 min after preparing cisplatin infusions. The lesions disappeared within 2 h. Open tests with both ammonium tetrachloroplatinate 0.25% and ammonium hexachloroplatinate 0.1% produced urticarial reactions after 40 min. Finally a handling test was also positive.

40.7.2 Contact Urticaria and Iridium

Iridium is a silvery-white transitional metal belonging to the PGEs. Iridium is a highly corrosion-resistant metal, even at very high temperatures, and only certain molten salts and halogens are corrosive to solid iridium. Although solid iridium is generally considered non-allergenic [33], finely divided iridium dust is much more reactive. Iridium has found usage as a hardening agent for platinum alloys as well as in dental practice due to its chemical resistance.

Bergman et al. [5] described the only case of contact urticaria caused by iridium in a 26-year-old man working in an electrochemical facility. His daily routines included coating of titanium anodes with various metal salts of the PGEs dissolved in hydrochloric acid. The coating solution was sprayed onto the anodes automatically. The patient initially developed respiratory symptoms. After 5 years of exposure, he also developed urticarial lesions on the wrists that would appear within minutes after exposure and clear completely within hours after exposure seized. Application of iridium salts to normal skin produced an urticarial reaction. Skin prick testing with increasing concentrations of iridium chloride gave a positive reaction to 0.05%, and a scratch test resulted in an anaphylactic reaction which was treated successfully with corticosteroids, antihistamine, and adrenaline. Skin prick tests with platinum salts were negative. The patient subsequently left his job due to the risk of developing a new anaphylactic reaction, and following this his symptoms disappeared.

40.7.3 Contact Urticaria and Palladium

Palladium also belongs to the group of PGEs. It is a rare, inexpensive silvery-white metal, which is less resistant to corrosion than platinum. The main uses for palladium are in electrical components and as a catalyst. Small amounts are used as a whitener for white gold in jewelry [21]. Although delayed contact allergy to palladium is common, and almost always seen concomitantly with nickel contact allergy [34], immediate cutaneous hypersensitivity to palladium is rare.

A 50-year-old female laboratory technician [35] working in a catalyst research facility developed an immediate facial erythema when exposed to fine dusts of dried and powdered mixtures containing

palladium nitrate salts. In addition, during accidental spillage of the powder mixtures, urticarial lesions appeared on the contact sites of her forearms. The patient displayed positive skin prick tests with tetraamminepalladium(II) hydrogencarbonate 0.1% and 1% as well as tetraamminepalladium(II) nitrate 10%. Application of the two palladium salts to the forearm of the patient gave a positive open skin application test with urticarial wheals after 20 min. On standard patch testing, the patient was negative to palladium(II) chloride 2%.

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Metal Allergy and the Lungs

41

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41.1 Introduction

About 91 of the 118 elements in the periodic table are metals or metalloids. Some metals are ubiquitous in the environment of human life. The most significant exposure to metals occurs in industrial use. In certain occupations, exposure to dusts and aerosols containing metals is particularly important. Metal salts are widely used in electroplating processes, metal alloys, pigments, tanning of leather, and production of many chemicals. Significant exposure to metals takes place also during welding processes, construction, grinding, and metalworking [1]. Soluble metallic salts may penetrate the airways and be transported as metal ions into lung tissues. Exposure to metals is not confined to the work environment. Hobbies and domestic activities may lead to clinical sensitivity in susceptible individuals.

The role of metals in the induction of skin allergy (allergic contact dermatitis) has been well known for many years. It is generally recognized that some metals may have allergenic properties (e.g., nickel, chromium, cobalt). Other metals (e.g., lead, cadmium) do not show such activity, even at high concentrations. So far, the reasons for this difference have not been fully explained. It is also not clear why sensitization occurs only in some exposed persons and what factors predispose to allergy to metals.

41.2 Impact of Metals on the Immune System

At high concentrations, metals are usually immunosuppressive, whereas at low concentrations, they are often immunostimulative. For many years it was believed that, like other haptens, metal ions are recognized by T cells as complexes with major histocompatibility complex (MHC) molecules or as complexes with peptides presented by MHC molecules. Specific metal-binding sites in enzymatic proteins seem to play a role in the pathogenesis of metal-related allergic reactions. Thus far, however, researchers have failed to demonstrate "metal-peptide" connections recognized by specific T cells. Metal ion particles are smaller than those of other allergens and do not form stable covalent linkages. Therefore, the activation of immune cells by metal ions likely differs from that of classic haptens [2]. Some metal ions can alter the structure of Langerhans cells and thus lead to changes in the peptides presented by these cells via three possible mechanisms: oxidation of the side chains of amino acids, the formation of coordination complexes that modify the structure of proteins, and nonenzymatic hydrolysis of amide bonds. Changes in the polypeptide chain of

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proteins may affect the process of antigen presentation. The role of humoral responses in allergy to metals is even less understood. Allergen-specific IgE (a-s IgE) to some metals (nickel, chromium, cobalt, platinum) has been identified in exposed workers, but their role in the pathogenesis of metal-induced asthma (MIA), except platinum-induced asthma, has not been elucidated. Therefore, the pathophysiological mechanism of MIA is still poorly recognized. The role of immediate and delayed type allergy (and/or other mechanisms, such as immunotoxic mechanisms) in this disease is unclear.

A new interesting and yet unexplored issue is the impact of metal nanoparticles on the immune system. Gas metal arc welding processes are able to generate significant levels of nanoparticles [3]. Ding et al. described the effect of metallic (tungsten carbide/cobalt) nanoparticles on the production of free radicals and the activation of cell signaling pathways in murine epidermal cells. Metal particles may activate the transcription factors, AP-1 and NF-κB, with stimulation of mitogen-activated protein kinase (MAPK) signaling pathways [4]. Copper oxide nanoparticles aggravated the development of asthma and increased inflammatory cell infiltration into the lung, as well as mucus secretion, in asthmatic mice via MAPK phosphorylation [5]. Also, zinc oxide nanoparticles induced eosinophilic inflammation in mice [6]. The influence of silver nanoparticles on allergic airway inflammation was investigated by Park et al. The authors showed these particles caused airway hyperresponsiveness, increased levels of IL-4, IL-5, and IL-13, and increased NF-κB levels in the lungs after ovalbumin inhalation [7].

41.3 Metals and Airway Diseases

Several forms of pulmonary toxicity or immunologic conditions (including acute and chronic obstructive syndromes) have been noted after exposure to metals. Inhalation of fumes or dusts containing various metallic salts may cause many airway diseases (Table 41.1). Some of them may mimic asthma and should be taken into consideration in the differential diagnosis.

Table 41.1 Lung diseases due to exposure to metals

Disease	Etiologic factors
Chemical tracheobronchitis	Many metals at high concentrations
Chemical pneumonitis/ adult respiratory distress syndrome (ARDS)	Many metals at high concentrations
Chronic obstructive pulmonary disease/ pulmonary emphysema	Cobalt, aluminum, manganese, titanium dioxide, beryllium, cadmium (chronic exposure)
Metal fume fever	Zinc, copper, magnesium, cadmium, aluminum, antimony, iron, manganese, mercury, nickel
Chronic beryllium lung diseases	Beryllium
Hard metal disease (cobalt lung)	Cobalt
Immunological asthma	Platinum, nickel, chromium, cobalt
Nonimmunological asthma (reactive airways dysfunction syndrome (RADS))	Many metals in high concentrations
Pneumoconioses (collagenous and non-collagenous)	Aluminum, tin, barium, iron
Cancer	Beryllium, chromium, cadmium, nickel

Workers are rarely exposed to pure metals, while their exposure to metal salts (sulfides, oxides, carbides, hydrides, and others) is quite common. Metals also form coordination complexes with ligands (sulfur molecules, ammonia, cyanogen, organic nitrogen). Bioavailability of such compounds and complexes is an important determinant of the possible effects on the respiratory system resulting from exposure to metals.

41.4 Metal Allergy in Asthma

Occupational asthma-like symptoms induced by inhalation exposure to metals were first described by Georgius Agricola, who published *De Re*

Metallica in 1556 [8]. Although the number of reported cases of MIA and metal-induced allergic rhinitis is relatively small, reports concerning the importance of metals as inhalant allergens are growing steadily [9, 10]. Almost all reported cases have been related to occupational exposure. However, some data indicate an association between environmental exposure to ambient metals (manganese, nickel, chromium, lead) and the development of asthma [11, 12]. There are very few epidemiological studies on the prevalence of airway allergy to metals. According to the program Surveillance of Occupational Respiratory Diseases in South Africa (SORDSA), platinum was the third most common agent causing occupational asthma in South Africa (12.3%) [13]. Because of the fact that occupational exposure to metals affects a large number of employees, it is likely that the disease may be underdiagnosed, especially when we remember that the diagnostic capabilities for airway allergy to metals are limited.

Occupational asthma from sensitization due to inhalation of metal-containing fumes or aerosols has been reported mainly in electroplaters, welders, construction workers, and metalworkers exposed to metalworking fluids. Asthma has been reported in workers exposed to various metals. The main metals which may cause MIA belong to the group of "transitional metals" located between group IIA and III in the periodic table (Table 41.2), although not all asthmogenic metals belong to that group. The biological activity and impact of transitional metals are predicated on their abilities to change oxidation states by oxidation (loss of electrons) and reduction (gain of electrons). As transition metals are electrically stable in more than one oxidation state, they play important roles in the catalysis of biologic oxidation reactions [1].

Table 41.2 Transitional metals that can induce asthma

Group of transitional metals	Metals that can trigger asthma
I ("iron group")	Vanadium, chromium, cobalt, manganese, nickel, zinc
II ("palladium group")	Ruthenium, rhodium, palladium
III ("platinum group")	Platinum, iridium

41.5 Diagnostic Challenges for Metal-Induced Asthma

Metals may exhibit different biological activities. Distinguishing between nonspecific (irritant) and specific (allergenic) effects of metals on the respiratory system is difficult. Most of the dust and aerosols containing these elements at high concentrations may cause irritant effects. Only a few metals may cause asthma via an immunologic mechanism. Therefore, asthma induced by metals could be immunologically mediated, or due to irritation (nonimmunological irritant-induced asthma; reactive airways dysfunction syndrome (RADS)). Moreover, in many workplaces there is exposure to a wide variety of metals. There are few workplaces where irritant-induced asthma due to metal compounds has been described in the absence of other irritants. Therefore, in some cases it is unknown which of these is the causative agent. For this reason, occupational asthma due to metals is characterized by significant diagnostic difficulties, especially for medical certification purposes. The incidence of this form of asthma may also be underestimated. Specific diagnostic difficulties relate to welders. Welding processes produce fumes consisting of gaseous and aerosol by-products composed of metals, metal oxides, and volatile chemical compounds. Stainless steel and mild steel are the most common wire types used in welding. In addition to exposure to dust and fumes containing various metals, welders are exposed to coating materials. These coverings have been known to contain epoxy resins, acrylics, phenol, formaldehyde, isocyanates, polyvinyl chloride, and various nanoparticles [14].

In most publications (epidemiological studies and case reports) the diagnosis of occupational asthma due to metals was based on questionnaire and spirometry examinations or bronchial challenge tests [15–18]. Such methodology is not

able to exclude nonspecific irritant effects. Much more reliable diagnoses are based on the clinical response to placebo-controlled specific challenge tests with metals at small concentrations (0.1% aqueous solutions or less) and concomitant evaluation of the accompanying changes (influx of inflammatory cells such as eosinophils and basophils) in the biological material (induced sputum and nasal or bronchial lavage fluid). The placebo-controlled specific inhalation challenge is generally regarded as the gold standard in the diagnosis of occupational asthma. The presence of metal-specific IgE in the serum or skin does not by itself indicate clinical response to the allergen and could be only a biomarker of exposure [1, 19].

41.6 Metals Causing Immunologic Occupational Asthma

41.6.1 Platinum

Platinum salts are among the most prominent allergens that cause immunologic occupational asthma and allergic rhinoconjunctivitis. Exposure to platinum is limited to certain industries (precious metal refineries, automobile exhaust catalyst production) and countries (mainly the Republic of South Africa). Platinum salt allergy is a considerable health problem in some chemical plants, with high cumulative risks for sensitization. In bronchial challenges with platinum salt, immediate or dual responses have been observed. Laboratory tests aiming to identify a-s IgE (such as skin prick testing (SPT)) are a useful technique for surveillance and early detection of platinum salt-sensitized workers with asthma. A direct comparison between SPT and bronchial challenges has revealed that SPT has high sensitivity and specificity [20]. Radioallergosorbent test (RAST) procedures with platinum salts conjugated to different proteins or anion-exchange resin have been also used for the detection of platinum sensitivity (presence of a-s IgE in serum); however it is suggested that serum-specific IgE assays are less efficient than SPT [21, 22]. There are few reports on the natural history of platinum-induced asthma. According to Merget et al., 17 of 24 workers with this kind of asthma (71%) still reported symptoms 2 years after exposure cessation. SPT reverted to negative in three subjects, but this was not accompanied by reduced bronchial responsiveness to methacholine and platinum salts [23]. It has been suspected that persistence of platinum-induced asthma could be due to continued contact with platinum of former platinum workers, who retain small amounts of the metal on their clothing [24].

41.6.2 Chromium

Of particular importance are hexavalent chromium compounds, found in many workplaces, for example, in the construction industry (cement). They may have an elevated allergenic potential because they are more soluble and presumably have easier access into body tissues. The first supposed case of chromium-induced occupational asthma was described in 1931 by Smith in a worker exposed to ammonium bichromate [25]. The diagnosis in this patient was based upon a positive patch test. The case of an electroplater with asthma, rhinoconjunctivitis, and dermatitis, and positive reaction after scratch testing with potassium bichromate has been described by Joules [26]. Card published a case report of a female polisher in an electroplating shop with asthma and dermatitis. About 2 hours after intradermal testing with potassium dichromate, she developed a severe asthmatic reaction [27]. In five subjects with occupational asthma described by Olaguibel [28], positive bronchial challenges with chromium salt were observed. A case series of four subjects with suspected chromium-induced occupational asthma showed positive bronchial challenges [29]. Two of them demonstrated positive SPT with chromium sulfate. A cement floorer with work-related asthma and dermatitis to chromium was presented by De Raeve et al. [30]. The patient developed a severe bronchial reaction after the challenge; SPT was negative. Eosinophilia was demonstrated in bronchoalveolar lavage fluid after the challenge. Cases of chromium-induced occupational asthma

and allergic rhinitis were reported also by other authors, demonstrating that bronchoconstriction can be experimentally induced by inhalation of chromium containing aerosol [31, 32]. Some authors have reported serum-specific IgE antibodies to chromium [33, 34].

41.6.3 Nickel

Despite the large number of workers exposed to nickel salts, the occurrence of asthma induced by this exposure is uncommon. Most occupational asthma cases caused by nickel have been single case reports. Relatively few cases of nickel-induced asthma have been associated with or preceded by contact dermatitis, a frequent outcome of nickel sensitization [35]. No conclusions can be drawn regarding the association of nickel dermatitis and asthma due to the low number of reported cases. It has been shown that nickel ions bind to human serum albumin (HSA). Specific IgE antibodies to nickel HSA were demonstrated in a nickel-sensitized subject [36]. Many studies described positive SPT with nickel salt solutions in exposed subjects with asthma/allergic rhinitis symptoms [1]. Bronchial challenge (mainly with nickel sulfate) produced immediate-type, dual, or isolated late responses. Several of these patients also manifested an increase in bronchial hyperresponsiveness for varying periods after the nickel sulfate challenge. Employees are often exposed to nickel and chromium at the same time, and thus asthma to both metals has been described by a number of authors. Cross-reactivity to nickel and cobalt has also been suggested [31, 33, 37–39].

41.6.4 Cobalt

Asthma due to cobalt has been reported mostly in hard metal workers and diamond polishers. Cobalt interacts with oxygen to produce activated toxic oxygen species which may be important in the pathogenesis of airway changes. Kusaka et al. observed that 5% of hard metal workers had work-related asthma and reported 19 cases of occupational asthma due to cobalt. These patients developed positive bronchial challenge reactions to cobalt chloride (dual, immediate, or late reactions), but only two subjects showed positive patch test results [40]. Twenty-two cases of cobalt asthma were described in a cobalt plant in Finland. The diagnosis was based on inhalation challenge testing. SPT with cobalt chloride was negative [41]. Shirakawa et al. have described two case series of cobalt-induced asthma in the hard metal industry, showing positive bronchial reactions with cobalt chloride. The authors did not perform SPT but instead carried out intradermal testing with the same cobalt salt which showed positive reactions in six of eight cases. Patch testing was positive in two cases, and cobalt-specific antibodies were demonstrated in 11 of 12 cases [42, 43]. Kusaka et al. observed that the patients who had specific IgE antibodies to cobalt also exhibited lymphocyte proliferation responses when their peripheral blood lymphocytes were incubated with either free cobalt or a cobalt-HSA conjugate. Bronchoalveolar lavage fluid examination revealed an increase in T lymphocytes with an inverted CD4+/CD8+ ratio [44, 45]. These results suggest that cobalt-sensitized lymphocytes may play a role in the immunopathogenesis of some hard metal asthma cases. However, it should be noted that some asthmatic patients did not demonstrate either cobalt-specific IgE or sensitized lymphocytes.

We have published a case of airborne cobalt-induced anaphylaxis, contact urticaria, bronchial obstruction, and delayed skin allergy in a ceramic decorator. In this patient, positive results of SPT and patch testing with cobalt chloride were obtained. Cobalt-specific IgE was also detected in the serum [46].

Cobalt is also likely to cause hard metal disease (HMD, cobalt lung)—an interstitial pneumonia with clinical presentations resembling hypersensitivity pneumonitis and with the potential to evolve to irreversible fibrosis. Workers presenting with both HMD and asthma have been described. We described the case of a female dental technician with the simultaneous presence of cobalt-induced asthma and interstitial changes suggesting HMD [47].

41.6.5 Manganese

The first report of manganese-induced occupational asthma was described by Saakadze et al. in 1977 in the former USSR [48]. An in-depth analysis of that report revealed some issues that may have produced a false conclusion from the study. Authors used a 20% solution of manganese chloride for the provocation test, which seems to be too hypertonic for the inhalation test. It is plausible that such a solution could produce bronchial spasm due to its hypertonicity rather than an allergic reaction. Moreover, no placebo control had been performed which could confirm the specific nature of the bronchoconstriction. In 2008, we identified the first well-documented case of manganese-induced occupational asthma in a welder. Our diagnosis was based on the clinical response to a placebo-controlled specific challenge (with 0.1% manganese chloride solution) and the accompanying changes in induced sputum (an increase in the proportion of eosinophils, from 0% to 10%, and basophils, from 0% to 3%, in 24 h after challenge) [49].

41.6.6 Other Metals

There has been only one case report regarding iridium-induced occupational asthma, in a worker exposed to iridium chloride in an electrochemical factory manufacturing titanium anodes [50]. SPT with iridium chloride showed a positive reaction, but a specific challenge test was not performed. There has also been only one case report regarding asthma due to palladium salt. An exposed worker exhibited positive SPT to tetraamminepalladium chloride as well as a positive bronchial provocation test [51]. A case study of occupational asthma due to rhodium salt in an electroplater has been described. This patient showed positive SPT reactions and positive bronchial immediate-type reactions separately with rhodium and platinum salts. Sensitivity to rhodium was much higher than to platinum salt. Reaction to platinum was interpreted as co- or cross-reactivity [52]. There have been two case reports of occupational asthma due to zinc in electroplaters. Both patients showed positive SPT and bronchial reactions (but only immediate type) to zinc sulfate, with increased bronchial hyperresponsiveness after the exposure [53]. Although positive immediate tests were demonstrated in these cases, it is not certain that IgE-mediated mechanisms were involved.

41.7 Metal-Related Asthma of Unknown Immunologic Mechanism

Because of irritant properties, exposure to high concentrations of metal-containing aerosols or fumes may cause irritant-induced nonimmunological asthma without a latency period. This form of asthma is referred to as "reactive airways dysfunction syndrome" (RADS) [54]. In many cases, it is difficult to determine whether the bronchoconstriction is caused by irritation or sensitization. Therefore, diagnosis is difficult, and the resultant epidemiological data are not reliable.

The form of occupational asthma occurring in aluminum smelter workers is known as "potroom asthma." The components of the potroom environment include various substances: fluorides particularly in gaseous forms, aluminum, dust containing cryolite, sulfur dioxide, oxides of carbon, and particulate organic matter. Airway inflammation is a central feature of potroom asthma, but the causative agent and pathomechanism of this condition remain unknown [55–57].

Aluminum was documented as causing occupational asthma by Vandenplas et al. [58]. They described the case of a welder with work-related asthmatic symptoms reported to occur specifically on days he was welding aluminum. The diagnosis was based on a specific inhalation challenge that (according to the authors) excluded the role of irritant gases and other constituents. An immunologic mechanism, however, has not been confirmed.

Information about vanadium-induced asthma is available only from case reports [59]. The cases associated with the cleaning of oil tanks were called "boilermaker's bronchitis/asthma." Occupational exposure to vanadium pentoxide is

primarily an inhalation hazard causing irritation of the respiratory tract. Positive SPT results or any other immunological findings have not been described. There are no reports of controlled laboratory challenges to vanadium.

41.8 Prevention of Metal-Induced Asthma

Personal protective equipment (masks) and appropriate ventilation can prevent the penetration of metal particles into the airways. While exposure reduction may be a rational approach to the management of subjects with irritant-induced asthma due to metals, this is rarely effective for workers with occupational asthma caused by a sensitizer. A smoking habit has been shown to increase the risk of lung function impairment in workers chronically exposed to metal fumes (e.g., welders). A tobacco smoking habit has been demonstrated to play a role in airway allergy to platinum [60, 61]. Therefore, platinum-exposed workers should be encouraged to stop smoking. The effectiveness of secondary prevention by medical surveillance programs in metal-exposed workers (at precious metal refineries) has been demonstrated. It has been shown in platinum salt-exposed workers that immediate removal from exposure after SPT conversion from negative to positive resulted in a good prognosis and positive-to-negative SPT reversion [62].

Although MIA is relatively rare, it should prompt occupational health and safety services to improve diagnostic and medical certification procedures and health risk management (prevention).

41.9 Other Manifestations of Metal-Induced Lung Diseases

41.9.1 Beryllium

Beryllium is a steel gray, lightweight metal which, due to its physical properties, has several important industrial applications. Beryllium is used mainly in alloys with aluminum, copper, iron, and nickel. Workplaces with potential sources of beryllium exposure include fluorescent lamp and neon sign manufacturing, the aerospace industry, automotive parts, the defense and weapon (including nuclear) industry, electronics, telecommunication, foundries, and beryllium extraction plants. Historical data suggest that daily-weighted average beryllium exposure levels could sum up to >50 μg/m^3 during the mid-1960s and to >30 μg/m^3 during the mid-1970s. At present the time-weighted average concentrations are in the range of 0.01–1 μg/m^3. Exposure to beryllium is mostly hazardous via the cutaneous and inhalation routes as this metal and its compounds are poorly absorbed from the gastrointestinal tract. In general, inhalation exposure to beryllium compounds results in long-term storage of appreciable amounts of beryllium in lung tissue, particularly in the pulmonary lymph nodes and in the skeleton. Exposure to beryllium may induce several clinical manifestations ranging from skin changes (edematous, erythematous, and papulovesicular dermatitis, granulomatous necrotic changes, and ulcerations), acute toxicity (irritation of the skin, eye, nose, and throat, inflammation, and pneumonitis), beryllium sensitization (BeS), and chronic beryllium disease (CBD) [63].

Several epidemiological studies showed that the prevalence of BeS ranged from 1.0 to 16.2% of workers exposed to beryllium, and 0.0 to 11.0% of subjects developed CBD [64]. The risk of developing BeS/CBD is dependent on genetic predisposition, with major histocompatibility complex human leukocyte antigen (HLA)-DPB1 Glu69 and Glu71 known to be significant risk factors (odds ratio > 10). The proportion of BeS that progresses into CBD varies from 10% to 100%. It seems that the risk of progression of BeS into CBD is the highest in the early years; however, there are cases of CBD diagnosed 10 to even 40 years after the first exposure [65]. Duration of exposure and the threshold values for beryllium are of course important risk factors. More cases of BeS/CBD were reported in the 1970s and 1980s, times of high occupational exposure, and a significant decrease in BeS was found after comprehensive preventive programs were introduced [64].

The immunopathology of BeS/CBD includes several steps. After the inhalation of beryllium, antigen-presenting cells expressing MHC molecule HLA DP Glu69 or Glu71 present beryllium (probably bound to albumins as a typical hapten) to naïve CD4+ T cells, which results in the activation, proliferation, and production of several Th1-type cytokines, including IFN-γ, IL-2, and TNF-α. This cytokine mixture promotes macrophage accumulation, activation, and aggregation, which induce the development of typical noncaseating granulomas, similar to those found in sarcoidosis. The distribution of granulomas within the lung tissue mimics the pattern seen in sarcoidosis, including the subpleural areas, bronchovascular bundles, and interlobular septa. In some cases, fibrosis may develop. Beryllium-containing particles can be demonstrated within granulomas; however, this is not necessary for the diagnosis.

The primary diagnostic tool is the beryllium lymphocyte proliferation test (BeLPT). This test should be performed in experienced centers. Mononuclear cells isolated from peripheral blood or bronchoalveolar lavage (BAL) fluid are cultured in the presence of different concentrations of beryllium salts. A positive test result confirms beryllium sensitivity (BeS). Of note, it has been suggested that beryllium patch testing may not be recommended as a diagnostic tool, as this may lead to sensitization in beryllium-naïve individuals [64].

The typical clinical manifestation of lung pathology in workers exposed to beryllium includes chronic beryllium disease (CBD) in a form of granulomatous lung disease sharing several similarities to sarcoidosis (Table 41.3). The natural history of CBD is variable. In most described cases, mild airflow limitations and a slow decline in diffusing capacity are seen. Clinical symptoms comprise dyspnea, cough, and decreased exercise tolerance.

Table 41.3 Characteristics of sarcoidosis and chronic beryllium disease

Characteristic	Sarcoidosis	Chronic beryllium disease
Triggering factor	Unknown	Beryllium exposure
Primary diagnostic tools	Clinical picture, radiological picture, lung or other tissue biopsy	Beryllium lymphocyte proliferation test
Beryllium lymphocyte proliferation test	Normal	Abnormal
Onset	Acute (Löfgren's syndrome) or insidious	Insidious
Isolated hilar lymphadenopathy	Common	Rare
Extrapulmonary manifestations without pulmonary involvement	Common	None
Ophthalmologic manifestations	Conjunctivitis, uveitis, retinal involvement	Conjunctivitis only
Erythema nodosum	Yes	No
Lupus pernio	Yes	No
Neurologic involvement	Central or peripheral nervous system	None
Cardiac involvement	Occasional	Rare
Hepatic involvement	Common	Occasional
ACE (angiotensin-converting enzyme)	Increased in serum	Increased in 22–75% of patients
BAL (bronchoalveolar lavage)	Lymphocytosis common (>20%)	
First-line therapy	Systemic corticosteroids (20–40 mg/daily) only in progressive disease	
Other therapies	Steroid-sparing agents may be considered (methotrexate, azathioprine, cyclophosphamide, infliximab(?))	
Prevention	Unknown	Possible (personal protective equipment, ventilation, workplace control of exposure)

Rarely, rapid progression, including fulminant pneumonitis, or slow but irreversible advancement into fibrosis and a restrictive pattern in lung function are reported. Diagnostic criteria for CBD include confirmation of an immune response to beryllium (BeLPT) and granulomatous lung inflammation on lung biopsy. Radiographic findings are similar to those found in sarcoidosis; however, hilar or mediastinal lymphadenopathy (very typical for sarcoidosis) is rare in CBD. It is recommended that all patients with a clinical and radiographic picture of sarcoidosis are carefully questioned for potential occupational exposure to beryllium. Additional workup includes bronchoscopy with BAL and transbronchial (ultrasound-guided) biopsies.

Patients with BeS/CBD should be followed up at experienced clinical centers. In progressive cases (based on lung function or radiology), immunosuppression with systemic corticosteroids (prednisone 20–40 mg daily) is the first-line therapy; however, this recommendation is likely based on experience from sarcoid patients as no clinical trials in this cohort of patients were published. Steroid-sparing agents, similar to other interstitial lung diseases, may be of use in some cases. Prevention programs to control exposure to beryllium should be considered in all facilities where this metal is in use, with the goal of limiting inhalational and skin exposures with elimination, substitution, engineering control, personal protective equipment, and other measures. The reduction of exposure to beryllium has been proven to reduce the incidence of BeS and, as a consequence, likely CBD [64].

41.9.2 Copper Sulfate

Several cases of vineyard sprayer's lung disease have been identified and described in vineyard workers who used the "Bordeaux mixture" containing copper sulfate and slaked lime. The mixture is used as a fungicide to prevent infestation of downy mildew or powdery mildew in vineyards. The Bordeaux mixture may induce several forms of lung disease, with the most typical being hypersensitivity pneumonitis and foreign body-type granulomas [65].

41.9.3 Other Metals

Occupational exposure to other metals may induce several manifestations of lung pathology. Zirconium alloys are used in electronic industries, as a powder for polishing, and in ceramic factories. Zirconium may cause granulomatous skin disease, and some reports of granulomatous pulmonary hypersensitivity, allergic alveolitis, granulomatous pneumonia, and a disease similar to sarcoidosis/chronic beryllium disease with the confirmed presence of zirconium particles within granulomas have been published [65]. Similarly, single cases of granulomatous lung disease have been found in workers exposed to titanium and aluminum. Indium, a soft metal, is mainly used nowadays as indium oxide or indium tin oxide as a conductive coating in electroluminescent panels. A few cases of interstitial lung disease and pulmonary alveolar proteinosis (PAP) have been reported in workers involved in the production of plasma TV and monitors. Pulmonary alveolar proteinosis is characterized by accumulation of pulmonary surfactant within alveoli, interfering with gas exchange and resulting in significant restriction, reduced diffusing capacity, and a typical "crazy paving pattern" on CT scans. In sporadic cases, whole-lung lavage as a treatment is usually effective, which seems not to be the case with subjects exposed to indium. Based only on limited case reports, the role of autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) remains unclear. The disease seems to progress despite limiting exposure to indium, and some fatalities have been reported [66].

Nowadays, there have been advances in science and nanotechnology implementing nanoparticles (defined as particles between 1 and 100 nanometers in size), with potential applications in electronics, optics, and medicine. Several

materials are used to create nanoparticles, including silicon, zinc oxide, carbon, gold, silver, titanium, and other metals. Physiochemical properties of nanoparticles, including small size, a high surface to volume ratio, high reactivity and catalytic properties, and the ability to pass through cell membranes, make them potentially harmful to biological systems. Several studies suggest that potential occupational exposure and nanoparticles as components of air pollution (e.g., automotive pollution produced by abrasion of catalyst materials in car exhaust systems) may be harmful to the health, although this has not been fully elucidated to date [67].

41.9.4 Hard Metal Lung Disease (HMLD)

Cobalt is a metal well known due to cobalt-based blue pigments used since ancient times in pottery manufacturing. Nowadays cobalt is mainly employed in the preparation of magnetic, wear-resistant, high-strength alloys. Cobalt sintered together with tungsten carbide is used for the grinding of other metals, including metal tools. Inhaled exposure to cobalt dust may lead to the development of a wide spectrum of lung disease, known as hard metal lung disease (HMLD). The typical clinical manifestation includes giant cell interstitial pneumonitis (GIP), with the most characteristic multinucleated giant cells engulfing other cells (macrophages and neutrophils) present in the air spaces and interstitium. These giant cells may be found in BAL or in histological lung tissue samples and are regarded as pathognomonic for GIP due to hard metal exposure. Other rare lung manifestations of cobalt exposure may present as desquamative interstitial pneumonia or bronchiolitis obliterans organizing pneumonia. Hard metal disease shares some similarities in clinical symptoms and radiology with chronic beryllium disease (CBD). In contrast to CBD, avoiding further exposure at the early stage of the disease may result in significant improvement or total remission; however, substantial fibrosis in advanced disease is not reversible [68].

Key Points

- Several metals with increasing industrial applications and thus potential occupational exposures may induce diseases of the upper and lower respiratory tract, with clinical presentations of asthma, rhinosinusitis, acute bronchitis, acute pneumonitis, carcinoma, and interstitial lung disease.
- Few metals may cause immunological asthma, and they all belong to transition metals of the fourth (chromium, cobalt, nickel, manganese, zinc), fifth (rhodium, palladium), and sixth (platinum, iridium) periods of the periodic table.
- The pathogenesis of airway allergy to metals is relatively poorly understood. The underlying immune and nonimmune mechanisms involved in asthma caused by metals or metal salts are various and have not yet been fully elucidated.
- Laboratory tests (skin and serological tests, lymphocyte proliferation test) have limited value in the diagnosis of metal-induced immunological asthma.
- Specific inhalation challenge tests play a key role in the diagnosis of metal-induced asthma.
- In the case of beryllium, the most common manifestations of allergy in the lung include beryllium sensitization and chronic granulomatous lung disease.
- Other metals such as indium, zirconium, titanium, cobalt, aluminum, and copper sulfate may sporadically induce lung pathology.
- New industrial applications and new formulations of metals, including nanoparticles, may in the near future result in unpredictable health hazards.

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42 Metal Allergy and Palmoplantar Pustulosis

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42.1 Introduction

Palmoplantar pustulosis (PPP) is characterized by a chronic eruption of sterile pustules on the palms and soles. The disease affects mainly middle-aged and older women, but is also frequent in men [1]. The most characteristic associations are between PPP and smoking, thyroid gland dysfunction [2, 3], autoimmune comorbidities, and abnormal calcium homeostasis [1, 4]. Numerous consecutive studies have confirmed these associations [1, 4].

Skin lesions are predominantly localized to the palms and soles, but can spread to the lateral hands and feet. The primary lesions are sterile pustules on an erythematous and desquamative background. The lesions are sometimes painful and may negatively influence the affected patients' quality of life and even result in a job change if there is significant occupational irritant or mechanic exposure. Aside from this, psoriasis vulgaris and eczema-like lesions may also be found on other parts of the body [1, 5]. Nail lesions (similar to those observed in psoriasis vulgaris) are often present as well, and the most common are nail pitting, onycholysis, subungual pustules, and dystrophy [5, 6]. The differential diagnosis includes acrodermatitis continua of Hallopeau, palmoplantar pustular psoriasis, irritant contact dermatitis, pompholyx, and fungal infections [7].

42.2 Etiology

The etiology of PPP has remained a mystery, although past studies have suggested a possible association with psoriasis. PPP presents with genetic, histopathologic, and clinical features that are not present in psoriasis; however, the common coexistence of psoriasis vulgaris and/or positive family history for psoriasis indicates at least a close relationship between PPP and psoriasis, and, at present, there is insufficient data to exclude PPP from the psoriasis group. Notably, there is also evidence that PPP is driven by leukocyte infiltration with associated pustular lesions caused and/or exacerbated by metal exposure [8]. In a recent study, positive patch test reactions to several metals were found in patients with PPP [9]; patients with PPP are therefore not a homogeneous group. There are at least two major clinical subtypes of the disease: one subtype with a chronic course resistant to treatment and a second subtype characterized by flares of skin lesions and long periods of remission. The disease usually has a chronic and relapsing course and is resistant to treatment.

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42.3 Epidemiology and Associations

There are several descriptions of palmoplantar pustulosis in patients of different populations. The most precise data come from Swedish and Japanese studies, as well as Spanish studies [1, 4, 9–11].

Ericsson et al. [1] described patients with PPP in the Swedish population. The study group included 59 patients, 88% of whom were women. The onset of disease occurred between 15 and 66 years of age, with the peak between 30 and 50 years. A total of 50/59 (84.75%) patients had rapid remission of their disease (maximum 1 year), and nine (15.25%) had at least one remission after 1–6 years. Of 59 patients, 56 (94.92%) were active smokers and 8 (13.56%) patients had a history of thyroid gland dysfunction. Abnormal levels of at least one thyroid test were found in 17/39 (43.59%) cases. In addition, antigliadin IgA antibodies were found in 10/39 (25.64%) patients with PPP [1]. These results were confirmed in another study [10]. Antigliadin IgA antibodies were found in 17.9% of cases, and tissue transglutaminase antibodies were found in 9.6% of cases. Moreover, 7/123 (5.69%) patients suffered from celiac disease [10]. It was shown that patients with elevated antigliadin IgA antibodies and tissue transglutaminase values who adhered to the gluten-free diet experienced clearance or marked improvement of skin lesions. Improvement was slow and usually occurred within a few months or years. However, three patients with severe PPP without antigliadin IgA antibodies or tissue transglutaminase antibodies did not improve on the gluten-free diet [10]. The mechanism for the beneficial effect of the gluten-free diet on PPP is unknown. Tissue transglutaminase is expressed in the endothelium of the gut and in the basal layer of the epidermis. It could be speculated that the gluten-free diet decreases the expression of tissue transglutaminase, which may lead to decreased activation and proliferation of inflammatory cells in the dermis [10]. However, in another study in German patients by Weisenseel et al., the association between PPP and gluten sensitivity was not confirmed [11].

It also has been shown that in women with PPP, the calcium level was increased and parathyroid hormone level decreased in comparison with a control group [12]. Another study confirmed abnormalities in calcium homoeostasis in PPP and showed increased serum calcium values, decreased parathyroid hormone level, and low 1,25-hydroxyvitamin D3 values compared with a control group [13]. Interestingly, PPP was not shown to be associated with abnormalities in bone mineral density or osteoporosis [14]. The mechanisms and clinical significance of these high serum calcium levels are unknown [11, 14]. The results were not confirmed in other populations. Hagforsen et al. [12] suggested that patients with PPP are at higher risk of developing Type 2 diabetes (OR 8.7).

Japanese patients with PPP differed from Swedish ones. Akiyama et al. [9] studied a group of 469 patients. The onset of disease was between 9 and 80 years of age, with the peak at 43.3 in women and 44 in men. Interestingly, only 266/469 (56.72%) were women. Similarly, in another study, the percentage of women oscillated around 50% [10]. Akiyama et al. found that 138/469 (29.42%) patients reported psoriasis vulgaris lesions in other locations [9]. Chronic infections, with tonsillitis being the most common, were found in 173/469 (36.89%) patients. In Japanese publications, the role of tonsillitis was underlined as a causative factor for immunological processes leading to skin lesions. Many studies confirmed that tonsillectomy may have caused an improvement in skin lesions or even remission in some patients with PPP [15, 16]. Kubota et al. recently conducted an epidemiological study of psoriasis and PPP in the Japanese population using a national database [11]. They found that the national prevalence of PPP was 0.12% (95% CI, 0.12–0.12%). Interestingly, in patients with PPP, about two-thirds were female (male-to-female ratio, 0.53), and the average age was 55.5 years [11]. Japanese authors also tried to establish a causal connection between PPP and smoking. In one study, 74.7% of male patients smoked over 20 cigarettes per day in comparison with 37.2% of healthy individuals [9].

Patients with PPP may develop Sonozaki syndrome (pustulotic arthro-osteitis, PAO) [17]. It is characterized by a nonerosive aseptic arthritis of the mono- or oligo-arthritic type. The most characteristic feature is sternoclavicular involvement, but the disease can affect the spinal column and peripheral joints as well [17]. The majority of cases were described in Japan. In one study, 70/469 (14.9%) patients had PPP and concomitant PAO symptoms [9]; whereas in another study, 4.2% of patients presented with PAO alone [11].

As far as the Spanish population is concerned, Gimenez-Garcia et al. demonstrated a higher prevalence of tobacco use and thyroid gland dysfunction in a Spanish group of 17 PPP patients, as well as predominance of the disease among women [4]. Moreover, 7/17 patients reported a personal history of repetitive tonsillitis, which is a frequent finding in Japanese patients [4, 9].

Recently, Scottish authors carried out a retrospective study of comorbidities associated with PPP [17]. The main characteristics of the patients supported the existing literature [1, 4]: 78.1% of patients were women and 79.4% were tobacco smokers. The median age of onset was 47 years (range 18–74). It was also shown that 49.3% patients with PPP presented with dyslipidemia, 38.3% presented with hypertension, and 24.6% with ischemic heart disease [16].

Arthralgia and arthritis are common problems in patients with PPP. In one study, arthralgia was reported in 42.37% of patients; [1] in another study, psoriatic arthropathy was present in nine patients (12.3%) [16]. As described above, an association has been found with PPP and Sonozaki syndrome, as well as SAPHO (synovitis, acne, palmoplantar pustulosis, hyperostosis, osteitis) syndrome [9, 11, 16–18]. The differences between various populations of patients with PPP are intriguing and probably result from differences in genetic background [6].

42.4 Palmoplantar Pustulosis and Metal Allergy

Skin lesions caused and/or exacerbated by metals are well known. For example, various types of metal alloys are used in prosthodontic replacements for dental applications and, although these metallic materials are biocompatible, metal allergies have occurred. Documented presumed metal allergies from dental restorations include reactions to nickel, iron, cobalt, and zinc (Fig. 42.1).

The relation between PPP and metal allergy has been reported primarily in the Japanese population. Yanagi et al. [19] described a case of PPP presumed to be secondary to zinc allergy on the basis of clinical history, positive patch test reaction to zinc, characteristic histology, and positive

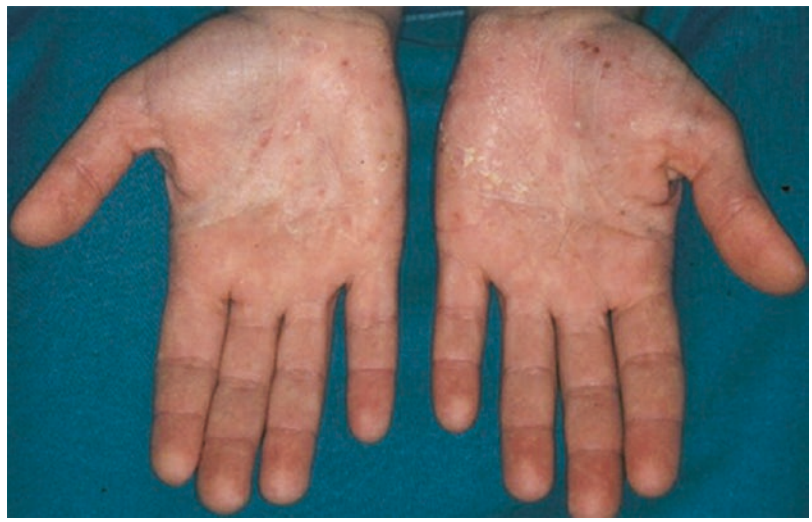

Fig. 42.1 Palmoplantar pustulosis, histologically confirmed, likely caused by cobalt contained in dental amalgam fillings

drug lymphocyte stimulating test (DLST) index. Histologically, identical pustules were found to be induced by zinc patch testing, and a complete remission was achieved by removal of zinc dental restorations.

Cobalt is present in cobalt chromium alloys and has also been implicated in PPP. For example, Song et al. [20] reported an unusual case of PPP on the hands and feet of a 58-year-old male patient caused by a cobalt allergy. The patient developed PPP, characterized by redness, pustules, vesicles, and scaly erythema on his hands and feet, 1 month after having cobalt chromium alloy cast crowns placed on his molar teeth. Skin manifestations persisted for 1 year. He underwent standard patch testing, which showed a strong positive reaction to cobalt chloride. After the crowns were removed, the skin manifestations disappeared in 3 weeks. In this case, there was a strong relationship between the appearance of PPP and metal exposure, as well as improvement after removal of the oral metal.

Two cases of PPP were reported from China that resolved after removal of oral metallic material [21]. Both patients were patch test positive to nickel and one also to cobalt. Both patients showed no recurrence of clinical findings or symptoms during a 1-year follow-up. A case of PPP dramatically exacerbated by a strongly positive patch test reaction to nickel has also been reported [22].

In North America, 9 of 15 patients with PPP who had undergone patch testing showed positive results, including to nickel and mercury, which were of unclear clinical relevance. The authors suggested that it might be prudent to routinely patch test PPP patients since the rate of patch test positivity was higher than would be expected in the general population [23]. In another study, 8 of 22 PPP patients had positive patch test results to one or more of 16 tested metals, with 6 of the 8 reacting to more than 2 metals. Positive results were seen to iridium, nickel, aluminum, palladium, selenium, iron, gold, chromium, zinc, silver, platinum, chromium, copper, zinc, and manganese. Replacement of dental metal with resin in these patients resulted in the remission of PPP [24].

In four patients with PPP in whom blood mercury levels were elevated, a seafood-free diet and chelation with a lowering of blood mercury levels and a clearing of the disease was reported [25]. As mentioned above, an increased occurrence of PPP in patients with psoriasis has been noted, as well as some histopathologic similarities, and it is interesting to speculate that mercury could have been a cause of the PPP in psoriatic patients because mercury was used extensively, both topically and parenterally, in the treatment of psoriasis in the first half of the twentieth century.

Nakamura et al. [8] evaluated the significance of leukotriene (LT) B in the formation of pustules of PPP in metal allergic patients. Pustular and plasma levels of LTB were measured prior to and 48 h after metal patch testing, and the mean levels of LTB in both plasma and pustules 48 hours after patch testing were significantly higher than before testing. Positive metal patch test reactions were detected in all seven PPP patients, to nickel, cobalt, platinum, tin, iron, and palladium. Palmoplantar pustules worsened 48 h after metal patch testing in all patients. The authors concluded that metals may play a role in the pathogenesis of PPP by contributing to the induction of high LTB concentrations in the pustules.

42.5 Conclusions

PPP is associated with moderate-to-severe discomfort and disability and is difficult to treat, often requiring the use of immunosuppressive agents. The etiology of PPP has remained unclear, and past studies have suggested a possible association with psoriasis, or an allergic reaction to metals such as zinc, cobalt, nickel, mercury, and others.

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Systemic Nickel Allergy Syndrome

43

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43.1 Introduction

43.1.1 Prevalence of Nickel Allergy

Nowadays, nickel is the most important worldwide contact sensitizer, and in recent decades, a constant increase in nickel dermatitis, corroborated by positive patch tests, has been observed in parts of the world especially among female patients. There are some risk factors that favor the onset of contact allergy: first of all, the inherent sensitization potential of the hapten, but also the frequency and duration of exposure, the presence of occlusion, any skin penetration-enhancing factors, altered skin barrier function, and environmental nickel pollution [1, 2].

Nickel sensitization can induce three forms of diseases: allergic contact dermatitis (ACD), mediated by a type IV immune reaction; respiratory allergy (RA), mediated by a type I immune reaction; and systemic nickel allergy syndrome (SNAS), whose pathogenesis, still not completely understood, involves both Th1 (typical of ACD) and Th2 (typical of RA) cytokine patterns.

RA to nickel, typically manifesting as asthma and rhinitis, is a relatively rare IgE-mediated disease; it essentially affects nickel-exposed workers (welders in particular) who become sensitized in the workplace. In contrast, ACD is a frequent disease, affecting nearly 15–20% of the general population [3]. A comprehensive review of all the epidemiological surveys conducted from 1966 to 2007 in Europe and the USA revealed a prevalence of nickel allergy ranging from 2.5% (Germany, 1966) to 17.6% (Norway, 2007) [1], with a higher prevalence among women than men (mean 17.1% versus 3%, respectively). A subset of patients affected by ACD also suffer from gastrointestinal and cutaneous symptoms after ingestion of foods containing a high quantity of the metal. Few studies in the literature report the incidence of SNAS, which is thought to affect approximately 20% of ACD patients [4, 5].

43.1.2 Systemic Symptoms in Nickel Allergy

In the 1970s, some authors noted that a considerable number of nickel-sensitive patients had dermatitis at sites other than those that were in direct contact with nickel-plated items. Christensen [6]

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was the first author to suspect that ingested nickel could be responsible for these reactions. The most common clinical manifestations were eczematous lesions at the elbow and knee flexures, eyelids, neck, and inner thighs; recurrent vesicular dermatitis of the palms, sides of the fingers, and/or soles of the feet; symmetrical nummular eczema, and anogenital eczema. It was also noticed that the hand eczema that so often followed the sensitization to nickel, usually starting some years after the first signs of metal sensitivity, most commonly appeared as volar, vesicular, symmetric pompholyx and showed activity independent of metal handling.

These data were confirmed studying patients with nickel-containing dental [7] and orthopedic [8] prostheses suffering from generalized eczema and urticaria.

In the following decades, there were many reports of nickel ACD patients suffering from cutaneous symptoms after ingestion of nickel-rich foods, especially vegetables. The histopathology of the flare-up of eczema appeared similar to the findings of ACD. This clinical picture was initially attributed to an abnormal absorption/secretion of nickel. However, studies demonstrated that there were no differences in nickel absorption and elimination between healthy subjects and nickel ACD patients both reacting and not reacting to the nickel oral challenge [9, 10].

The condition was termed "systemic nickel contact dermatitis" [11, 12] or "hematogenous contact eczema" [13], and a dose-dependent relationship between nickel and the appearance of cutaneous symptoms was also observed. Subsequently, there were observations that the same patients reported also gastrointestinal disturbance (meteorism, abdominal pain, diarrhea, and constipation), and the term systemic nickel allergy syndrome was introduced as it better describes both the involvement of organs other than the skin and the implied immunologic mechanism that also involves Th2 in addition to Th1 cytokines (the latter of which are typical of ACD) [14].

Few works have addressed the clinical nosology of this syndrome, being limited to symptomatology described in case reports [15–17], in some therapeutic trials [18, 19] and as a result of oral nickel challenges [20]. Oral nickel challenges were performed at doses varying from 0.3 to 10 mg, and a definite dose-response reaction pattern to oral nickel exposure was observed among nickel-sensitive subjects. A systematic study was conducted in 2013 to define the clinical characteristics of these patients [4]. The study involved 361 nickel ACD patients, 144 of which had a positive history of systemic symptoms linked to the ingestion of nickel-rich foods. In particular, the patients reported variably associated ACD flare-up, flare-up of previous positive patch tests, widespread eczema (including involvement of regions without direct contact with the metal), urticaria, angioedema, meteorism, gastric acidity, abdominal colic, diarrhea, vomiting and reflux, cough, dyspnea, headache, chronic fatigue, and dizziness. SNAS was diagnosed in only 98 (27%) of patients by elimination diet (http://www.lofarma.it/it/allergie/index.html) and placebo-controlled nickel oral challenge (capsules made by Lofarma, Milan, Italy). Cough, dyspnea, headache, chronic fatigue, and dizziness, reported in the history by 30 patients as always associated with gastrointestinal symptoms, were never observed after the nickel oral challenge and therefore should not be considered as part of SNAS. Similar data have also been observed after very high dose (10 mg) nickel challenge [9, 10, 21]. Therefore, only cutaneous and gastrointestinal symptoms clinically characterize SNAS (Table 43.1).

Table 43.1 Cutaneous and gastrointestinal symptoms in SNAS patients

Cutaneous symptoms	Gastrointestinal symptoms
ACD flare-up	Meteorism
Flare-up at sites of previous positive patch tests	Gastric acidity
Widespread eczema (also in regions without contact with metal)	Abdominal colic
Urticaria	Diarrhea
Angioedema	Vomit and acidity to the throat

In SNAS patients, systemic symptoms followed a clinically evident nickel ACD of about 5 ± 3 years, irrespective of the severity of eczematous lesions or the degree of positivity of nickel patch tests. Skin and gut manifestations appeared almost always in combination, except for ten patients showing only cutaneous symptoms (ACD flare-up and widespread eczema) and eight patients with only gastrointestinal disturbance (meteorism and dyspepsia, combined with colic, gastric acidity, vomiting, diarrhea, or reflux). The most frequent manifestation of SNAS was the flare-up of previous ACD eczematous lesions reported by almost all patients, followed by a flare-up at the site of a previously positive nickel patch test. Such symptoms were variably associated with eczema in regions not in contact with the metal, or with urticaria and angioedema.

The majority of patients (73%) reported that systemic symptoms followed the ingestion of a single nickel-rich food, while other patients required a higher nickel intake to elicit symptoms. Similarly, almost all SNAS patients reacted to an oral challenge with the lowest nickel dose. Many authors criticize the usefulness of this test, as the dose of 1.25 mg is higher than that of a single nickel-rich food. In any case, the authors who studied the dose-response relationship of oral exposure to nickel in sensitive subjects found a very high sensitivity and specificity for the oral nickel challenge [11]. Challenged patients reacted to oral nickel exposure at doses ranging from 0.3 to 4 mg with increasing symptoms, while none of the healthy controls reacted.

SNAS is associated with lactose intolerance in a very high percentage of patients (63–74% from various studies) [4, 22]. It can be hypothesized that in SNAS patients the nickel-induced pro-inflammatory status could temporarily impair the brush border enzymatic functions, resulting in hypolactasia.

The incidence of other IgE-mediated diseases was similar to that of the general population, as 2 patients had atopic dermatitis, 29 had respiratory allergy to pollens and/or mites (8 asthma and 21 rhinitis), and 4 had allergy to latex and were also sensitive to latex cross-reactive fruits.

43.1.3 Pathogenesis of SNAS

Recent studies have clarified many aspects of the pathogenesis of SNAS. They especially have clarified that it is a nosological entity distinct from other forms of allergy to nickel. In particular, no IgE antibodies were found in SNAS patients, and there was evidence that involvement of the immune system was more complex than the type IV immune reaction seen in ACD.

Studies have focused on (1) nickel metabolism and (2) nickel immune response both before and after nickel challenge, comparing results obtained in SNAS patients, ACD patients, and normal subjects.

43.1.3.1 Nickel Metabolism

It has been estimated that the average human daily intake of nickel is approximately 200 μg and that a nickel dietary requirement of about 50 μg per day is important in human nutrition [23]. Most ingested nickel remains unabsorbed within the gastrointestinal tract and excreted with feces, and only about 1 to 10% is absorbed. Serum concentrations vary from 1.6 to 7 μg/L and urinary nickel concentration from 2 to 5 μg/L. The nickel concentration in sweat is high, ranging from 7 to 270 μg/L; thus, sweating may provide an important route for the excretion of nickel from the body. Furthermore, sweat, which may contain up to 20 times as much nickel as plasma, may influence the amount of nickel that reaches the skin [24].

It has been shown that urine is the most reliable parameter to follow after oral intake of nickel, even though both serum and urinary levels of nickel reflect the nickel intake [25]. Nickel blood concentrations vary greatly in different reports of oral challenge with the metal. It is known that many factors, including diet, stress, age, and seasonal variation, may influence serum nickel levels. In rats intravenously injected with nickel chloride, 90% was eliminated in the urine within 4 days postinjection, and only 3% was excreted by fecal discharge [26]. Nickel urinary excretion is rapid, not dose-dependent, and its elimination appears to follow first-order kinetics

[27]. Estimates of the half-life of urinary removal of nickel range from 20 to 60 h [28, 29].

Atopy seems to be a factor influencing nickel absorption and excretion; in fact, blood levels and nickel excretion were determined in patients with nickel allergy and different types of eczema with and without atopy before and after a single oral dose of nickel sulfate. Urinary excretion of nickel was found to be age dependent (decreasing with increasing age), and the level of nickel in urine was significantly ($p < 0.005$) higher in the atopy groups compared to the controls [30].

Only one study compared SNAS patients to ACD and non-allergic subjects. In this case, similar serum nickel concentrations in allergic patients and controls, both before and after metal ingestion, were observed among the three groups. Urine and serum nickel were in the range of the reference values (0.2 to 2.0 μg/L of serum or urine) at baseline. A similar peak of urine and serum concentrations was determined 4 h after the Ni challenge (5 mg), with a similar decrease after 24 h [21].

In conclusion, no alteration of nickel metabolism is present in SNAS patients.

43.1.3.2 Nickel Immune Response

It has been demonstrated that both Th1 and Th2 immune responses are involved in eliciting ACD. Analyses of cytokine production by Ni-specific T cells have demonstrated a mixed Th1- and Th2-type cytokine profile in both T-cell clones and peripheral blood mononuclear cells (PBMC) [31–34]. Analyses of Ni-specific T-cell clones generated from PBMC and the skin of allergic patients have also suggested that both CD4+ and CD8+ T cells are involved in the immune response to Ni [35, 36]. However, comparing among ACD patients those reacting to the oral administration of nickel (SNAS patients) versus nonreactors, a more specific immune involvement has been determined. The oral administration of nickel induced a decrease of blood CD8+CD45RO+ cells in both ACD and SNAS patients (this was significantly greater in SNAS patients, $p < 0.001$), whereas CD4+CD45RO+ lymphocytes significantly decreased only in SNAS patients [37–39]. These results suggest a migration of memory T cells from the blood to the peripheral tissues. In particular, there is evidence that CD4+CD45RO+ cells increased in the intestinal mucosa, particularly in the epithelium, in SNAS patients after nickel challenge. CD8+ cells, in contrast, decreased after nickel challenge in the gastric epithelium due to cell apoptosis [37].

NiSO4-stimulated peripheral blood mononuclear cells (PBMC) from nickel-allergic patients have been shown to produce increased levels of Th1 and Th17 cytokines and a variable increase in Th2 cytokines [32, 40–42]. In biopsies of positive patch test reactions taken from different skin sites in nickel-allergic patients, a statistically significant increased expression of mRNA for IFN-γ, IL-2, IL-4, and IL-10 was found [43, 44]. These findings partially contrasted with the results of previous studies with a similar design showing that a Th1 cytokine profile developed in such individuals [45–47].

When nickel ACD patients were divided between responders to oral nickel (induction of widespread eczema and gastrointestinal symptoms after oral nickel challenge) and non-responders, an increase in Th2 cytokines was exclusively seen in responders. In particular, IL-5 was the cytokine with the most relevant increase [10, 37, 38]. Cytokine production was also measured in therapeutic trials in SNAS, demonstrating that in such patients an overproduction of Th2 cytokines (IL-5 mainly but also IL-13 and IL-4) is characteristic of the disease and its modulation follows desensitization treatment, which also induces an increase in IL-10 [18–48].

In conclusion, available data indicate that, in SNAS patients, nickel challenge induces a mobilization of CD4+CD45RO+ cells from the blood to the gastrointestinal mucosa. Also, in addition to the Th1 and Th17 cytokines typical of nickel ACD, in SNAS patients there is an increased production of Th2 cytokines that is reversible after nickel desensitization.

43.2 Diagnosis

The diagnosis of SNAS requires a history of nickel ACD, the appearance of the above-described cutaneous and/or gastrointestinal disturbances following the ingestion of nickel-rich foods, and the disappearance or substantial improvement of such symptoms after a low nickel diet. Essential for the diagnosis is to confirm that symptoms reappear after a double-blind placebo-controlled oral nickel challenge. Nickel ACD should be diagnosed by the history and the results of a nickel patch test performed according to the International Contact Dermatitis Research Group criteria [49].

Symptomatic patients should be administered a low nickel diet. The nickel daily dietary intake has been estimated between 200 and 600 μg. A low nickel diet contains a maximum of 50 μg of the metal. A list of the nickel content in foods is provided in Table 43.2. The diet should be followed for at least 1 month, and patients who respond to this should undergo a nickel oral challenge.

The provocation test consists of administering a capsule containing talc as placebo or nickel sulfate at increasing doses from 0.6 mg. The oral challenge is performed in the morning, in individuals who have been fasting for 12 h. If the test is still negative, the nickel dose will be increased to 1.25, 2.50, 3.75, and 5.00 mg at 1 day intervals from the last dose. The skin status and systemic symptoms are evaluated and recorded 24 h after the challenge. Positive reactions include eczematous eruptions of previously unaffected skin, flare-up at previous sites of contact dermatitis, including flaring at sites of previous positive patch test reactions to nickel, and urticaria, angioedema, and/or gastrointestinal symptoms. Figure 43.1 shows two skin reactions after oral nickel challenge.

The diagnosis of SNAS is confirmed in the case of a positive challenge. In such cases, the low nickel diet can be used as treatment. However, the low nickel diet consists of a list of forbidden foods without a healthy balanced dietary plan. This regimen is difficult to follow not only because of its impact on the patient's quality of life, but also because nutritional characteristics of many nickel-containing foods (fiber, carbohydrates, essential elements and vitamins, etc.) are important for human health. For this reason, a nutritionally balanced diet with low nickel content [4] has been developed, also providing a list of allowed foods and a number of appropriate recipes (available at http://www.lofarma.it/it/allergie/index.html) to increase patients' compliance. Despite this, maintaining the diet for a long time strongly impacts the patient's quality of life. Therefore, desensitization treatment should be considered.

Table 43.2 Nickel content in foods

Ni 100 μg/kg	Ni 200 μg/kg	Ni 500 μg/kg	Ni > 500 μg/kg
Carrots	Apricots	Artichoke	Almonds
Lettuce	Broccoli	Asparagus	Chickpeas
Green Salad	Corn	Beans	Cocoa and derivatives
Liquorice	Eggplant	Cabbage	Concentrated tomato
Mushrooms	Lobster	Cauliflower	Lentils
Plaice and cod	Onions	Green beans	Oats
Rhubarb	Peppers	Integral flour	Peanuts
Rice tea	Pears	Yeast	Walnuts
	Raisins	Margarine	
	Zucchini	Mussels	
		Oysters	
		Potatoes	
		Peas	
		Plums	
		Spinach	
		Tomatoes	

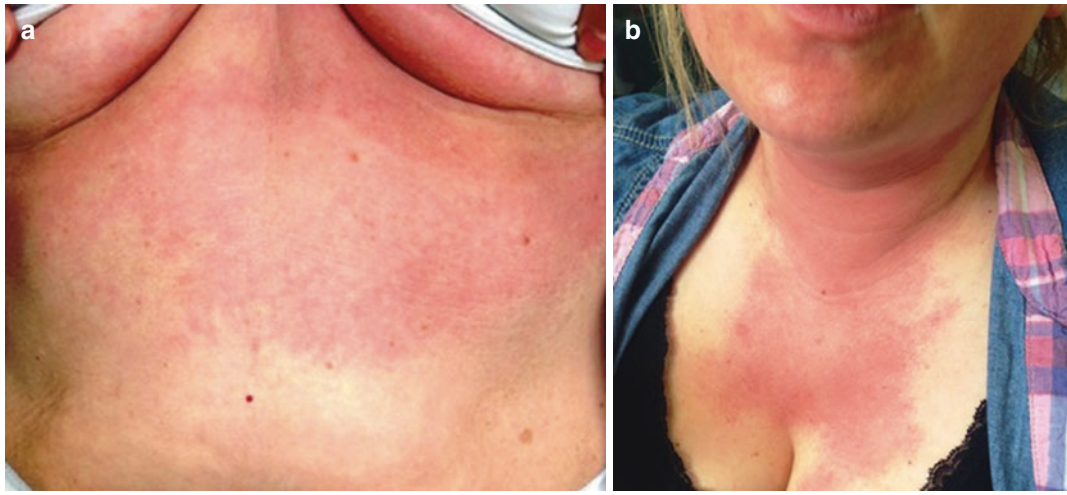

Fig. 43.1 (**a**) and (**b**) Examples of skin reactions after oral nickel challenge

43.3 Induction of Immunological Tolerance to Nickel

Continuous exposure to nickel may lead to oral tolerance mechanisms that modulate nickel sensitivity [50]. Many experimental studies have been made in animal models to study the induction of immunological tolerance to some antigens and haptens by repeated oral administration. The tolerance was mediated by T regulatory cells and suppressor lymphocytes [51, 52].

Tolerance to metals was also studied, in particular nickel and chromium. Animals treated via the oral route with nickel and chromium powder failed to react to subsequent immunization, whereas control animals not pretreated became clearly hypersensitive [53]. The results of these studies were confirmed in mice. After oral administration of nickel sulfate ($NiSO_4$) in drinking water for 10 weeks, treated mice were tolerant toward the subsequent sensitization step with $NiSO_4$, in comparison to the controls. CD4negCD8+ T cells were implicated in the mechanism of tolerance [54]. Moreover, some experiments demonstrated a long-term desensitization mediated by antigen-presenting cells (APCs), CD4-8+ T cells, and T regulatory cells. In fact, when splenic T cells or lymph node cells of orally tolerized mice donors were transferred to naïve recipients, even after a treatment-free interval of 20 weeks, they specifically prevented sensitization of the recipient mice. The lymph node cells of such donors were anergic, because in vivo sensitization with $NiCl_2$ and in vitro restimulation with the hapten did not induce IL-2 production that was seen in lymph node cells of mice not tolerant before sensitization [55]. Results were confirmed by subsequent studies showing that the oral administration of nickel (both as $NiSO_4$ and $NiCl_2$) to mice already sensitized to the metal was also able to induce a long-term persistent desensitization mediated by antigen-presenting cells (APCs), CD4-8+ T cells, and T regulatory cells. In fact, nickel oral administration induced T suppressor cells and tolerogenic APCs that were able to maintain tolerance when activated by the antigen in the presence of a danger signal [56]. These animal experimental studies were the basis for the use of a desensitizing treatment in humans.

The efficacy and safety of hyposensitization to nickel in humans were initially evaluated in patients affected solely by contact allergy. The first attempt was made by Sjoval and Coll [57] in 1987 who, having observed that patients with nickel ACD reported an improvement of their hand eczema and metal sensitivity after a positive oral provocation test with nickel salts, administered orally capsules containing 5 mg of NiSO4 to nickel-sensitized patients for 6 weeks; this

treatment led to reduction of the degree of contact allergy, measured as an increase in the lowest dose of NiSO4 able to induce positive patch test reactions before and after treatment. No effects were observed with a dose of 0.5 mg. Other studies showed contrasting results. Morris [58] reported clinical improvement in 85% of patients without tolerance to nickel during challenge tests who completed a sublingual hyposensitization treatment. Bagot et al. [59] did not obtain positive results in a double-blind placebo-controlled study involving patients who ingested 5 mg capsules of nickel sulfate per week for 7 weeks. On the other hand, the weekly subcutaneous administration of increasing doses (10^{-6}–10^{-3} mol/L) of a nickel sulfate-containing solution failed to show improvement in nickel ACD [60].

The first attempt to utilize the oral administration of nickel in patients with SNAS was made in 1995 [61]. The authors treated patients with ACD that showed systemic symptoms with ingestion of nickel-rich foods with increasing doses of oral nickel sulfate associated with an elimination diet. The oral administration of very low doses of nickel sulfate tablets (0.1 ng daily for the first year and then every other day for the second and third years) to 51 patients led to the disappearance of symptoms in 29 of the 30 patients who completed the treatment course [61]. These preliminary results were confirmed in 2006 [5] in a large clinical trial involving 214 patients affected by SNAS. A group of 136 patients were treated for 12 months with a very low dose of nickel (up to 0.2 ng per day) while following a nickel-free diet. The control group (78 patients) only followed a nickel-free diet for the same period. After 1 year, patients gradually resumed nickel-containing foods: the majority of the nickel-treated patients (94 out of 136, 69%) showed a clear clinical improvement in their condition, 47% even achieving complete remission with no sign of disease following reintroduction of nickel-containing food; in contrast, only a minority of the patients of the control group (17.9%) could reintroduce dietary nickel without showing symptoms. Patch tests and oral provocation tests were performed in both groups before and after desensitization. Control patients did not show any modification in reactivity to nickel either via patch testing or oral challenge. In treated patients, reactivity to nickel patch tests showed no variation in 68 cases (72.3%), decreased in 17 (18%), increased in 1 (1.1%), and turned negative in 8 patients (8.6%). The oral challenge test showed an increase in tolerance to nickel in the majority of cases: 29 (30.9%) did not react, 47 (50%) reacted to a higher dose, and 17 (18%) to the same dose, while 1 patient (1.1%) showed a decrease in threshold dose.

Oral nickel hyposensitization, with high doses of metal, has been proposed also for ACD patients; however, the clinical trials set up so far involved a limited number of ACD patients, and the treatment was administered for only a short period of time. The most recent clinical trial [62] studied 28 nickel ACD patients who received a daily dose of 50 μg of $NiSO_4$ in cellulose capsules for 3 months. In the 26 patients that completed the study, oral hyposensitization ameliorated clinical manifestations despite continued nickel exposure; moreover, the threshold of skin responsiveness to nickel increased, and the T lymphocyte responsiveness to the metal in vitro decreased. During the 1-year follow-up period, 50% of the patients experienced relapses of clinical manifestations at the sites of topical exposure to nickel, likely as a consequence of the short period of treatment.

The nickel doses used for hyposensitization treatment in the various studies were quite different, ranging from 1 ng to 5 mg, and not justified by investigative studies, until 2010 when it was established that SNAS patients tolerated 1.5 μg nickel/week without side effects, whereas ACD patients could receive much higher doses, up to 50 mg [18, 62].

At present, nickel hyposensitization in SNAS is administered at the cumulative dose of 1.5 μg/week and has proven to be effective in reducing symptoms and the need for medications. The treatment induces significant modulation of the immune system. The clinical benefits are maintained at least for 1 year, the longest period of follow-up that has been evaluated in controlled trials so far [18, 63].

The use of such treatment was validated by a phase III study conducted in 2014 [63] as a multicenter prospective double-blind placebo-controlled trial, in which 141 patients were randomly assigned to three treatments (1.5 μ g, 0.3 μ g, and 30 ng Ni/week) or placebo. The study involved patients who (1) had a positive nickel patch test, (2) reported symptoms suggestive of SNAS, (3) improved at least 70% from baseline after 1 month on a low nickel diet (severity of symptoms rated on a visual analog scale (VAS)), and (4) tested positive to a nickel oral challenge. The study lasted 1 year, and after 5 months, patients were allowed to progressively reintroduce nickel-rich foods, starting with those with a maximum of 100 mcg of nickel content.

The treatment was effective. During the reintroduction of nickel-rich foods, symptoms improved significantly in patients given the highest nickel dose compared to placebo, with a VAS score similar to that of patients on the low nickel diet. The effect of nickel oral hyposensitizing treatment (NiOHT) seemed dose-dependent, as 1.5 μg Ni/week gave the best results (Group 1), 30 ng Ni/week and placebo the worst (Group 3 and Group 4), and 0.3 μg Ni/week was intermediate (Group 2). Gastrointestinal symptoms significantly improved in parallel with VAS scores compared to placebo (Fig. 43.2), and were more sensitive to NiOHT than cutaneous manifestations, which decreased in frequency, but at the limit of statistical significance (p 0.05) compared to Group 3 and placebo. This is not altogether surprising, as skin contact with nickel, which can never be completely avoided, might have induced symptoms linked to ACD, confounding the results. The effectiveness of NiOHT with 1.5 μg Ni/week is corroborated by the observation that, during the reintroduction of nickel-rich foods, only three patients (10.3%) took rescue medications, compared to significantly more in other groups (Group 1 vs. each group, p 0.05). The subjective data, symptoms, and VAS ratings, which show post-NiOHT tolerance to nickel, are supported by objective tests such as nickel oral challenge and patch testing. As a matter of fact, at the end of treatment, significantly more patients in Group 1 than in Group 3 and the placebo group needed a higher nickel dose at the oral challenge to elicit symptoms than before treatment. Similar differences were found with patch testing at the end of the study: there were significantly more patch test negatives in Group 1 than in Group 3 and the placebo group (Fig. 43.3).

The efficacy of desensitization seems to be linked to an increase of IL-10 [48], a regulatory cytokine involved in the action of vaccines for inhalant and hymenoptera venom allergy [64]. These changes in regulatory cytokines led to the hypothesis that nickel tolerance after NiOHT might be a consequence of the differentiation and proliferation of nickel-specific T regulatory lymphocytes, which can maintain immune tolerance to nickel in healthy subjects [65]. This also can explain the effectiveness of the low nickel doses administered: high doses of antigen favor an anergy-driven pathway to tolerance, while low doses of antigen promote a suppressive pathway via regulatory T cells producing IL-10 and TGF-β [66, 67].

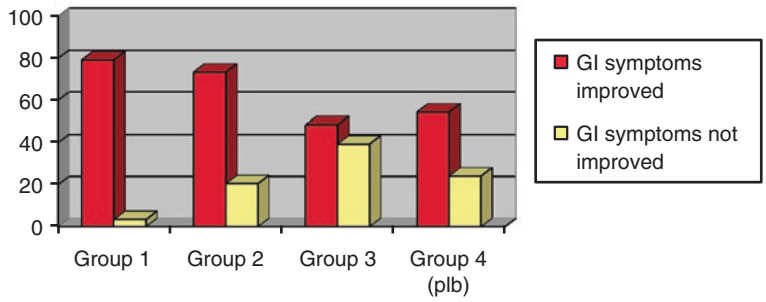

Fig. 43.2 Changes in gastrointestinal symptoms during reintroduction of nickel-rich foods. Patients of Group 1 were treated with 1.5 μg of nickel, Group 2 with 0.3 μg of nickel, and Group 3 with 30 ng of nickel. Group 4 received placebo

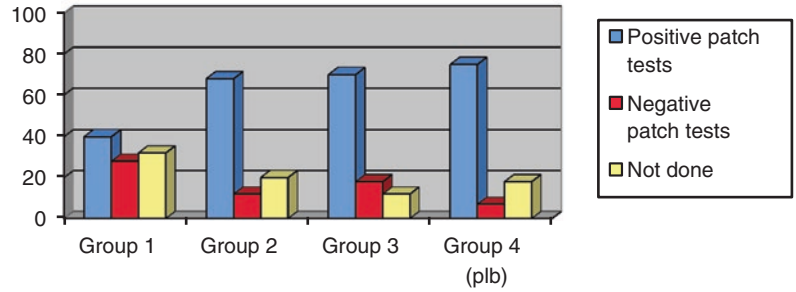

Fig. 43.3 Positive and negative patch tests in the four groups at the end of the study, showing a significant increase in negative patch tests in Group 1. Patients of Group 1 were treated with 1.5 μg of nickel, Group 2 with 0.3 μg of nickel, and Group 3 with 30 ng of nickel. Group 4 received placebo

43.4 Conclusion

SNAS can be defined as the appearance of cutaneous (in regions without direct nickel contact) and gastrointestinal symptoms after the ingestion of nickel-rich foods and is found in approximately 20% of nickel ACD patients. The diagnosis can be made in patients with ACD to nickel whose gut and skin symptoms disappear or improve after a low nickel diet. The gold standard for the diagnosis is the double-blind placebo-controlled oral challenge with nickel. The pathogenesis of the disease involves both Th1 and Th2 patterns of cytokines.

Nickel hyposensitization is effective in patients suffering from SNAS. The majority of such patients can safely consume nickel-containing foods after 1 year of treatment. Clinical experience with this regimen in ACD patients, although positive and encouraging, is scarce in terms of the number of patients treated and length of the hyposensitization course and is followed by a relapse of cutaneous symptoms after a relatively short period of time. In any case, nickel hyposensitization is able to modulate immune responses to nickel, restoring a state of tolerance that seems to be mediated by T regulatory lymphocytes. This is a promising area, and further research is required.

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The author name was inadvertently published as "By Trine Hilkjær Petersen" in the table of contents and chapter 9.

This has now been amended throughout the book as Trine Hilkjær Petersen

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