Metals

11

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Contents

Abbreviations

Au	Gold
Co	Cobalt
Cr	Chromium

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DMG Dimethylglyoxime
Ni Nickel
Pd Palladium
Pet. Petrolatum

11.1 Introduction

In the earth crust more than 50 metals are present, but from an allergy point of view, we mainly need to focus on nickel, cobalt and chromium, the three most common metals in contact allergy. However, also aluminium, copper, gold, palladium, platinum, rhodium and titanium have been described or discussed to cause skin sensitization. In this chapter a short review of clinically relevant information for nickel, cobalt, chromium and palladium in metallic items, metal compounds and in different types of materials and products is presented.

Metals may in their metallic state (as alloys or pure metal) or as ions act differently. Alloys are mixtures (without chemical bonding) of more than one element in metallic form. Often alloys are produced when you want to have the chemical properties of two or more metals or new unique properties of the alloy itself. Common alloys are, for example, copper-nickel, stainless steel (iron/nickel/chromium) and nickel-silver. Ions are released from a pure metal or an alloy upon contact with different solutions, for example, human sweat. The ions can penetrate the stratum corneum and cause sensitization and allergic contact dermatitis.

11.2 Contact with Metallic Items and Exposure to Metals

It is of great importance to understand that when it comes to contact allergy to metals, it is the surface of the material that is important and not the bulk material. This can be emphasised by thinking of how the skin comes into contact with the metals. For example, the hands are in contact with the surface and rarely the bulk material. On the surface of a metallic item, an oxide is present, and the composition of the oxide depends on which metals are present in the alloy. For example, stainless steel often has a very hard and corrosion-resistant surface due to chromium oxide that protects the bulk material, and to some extent it also prohibits skin deposition of nickel and chromium ions from touching the material. Although, concerning stainless steel, there are lower-grade compositions containing sulphur that may enhance the release of nickel ions [1]. Another example is from coins: nickel-plated coins will have a surface oxide consisting solely of nickel oxide/hydroxide, whereas a copper-nickel coin will have a mixture of copper oxide, nickel oxide/hydroxide and combinations thereof. When handling such coins, the pure nickel oxide will release more nickel ions on the skin than the mixed oxide will, mainly because nickel is present at a higher concentration at the surface. This will result in a higher amount of nickel per surface area on the skin from the nickel-plated coins than from the copper-nickel coins [2].

11.3 Exposure Times: Relevant for Elicitation of Contact Dermatitis

As soon as your hands touch a metallic surface, ions will be transferred to your hands. The skin dose can be assessed using acid wipe sampling. Using the method skin doses after touching work tools and work materials has revealed that already after 30 min to 2 h nickel, cobalt and chromium were present on the skin in doses able to elicit contact dermatitis. Several short and repeated contacts with metallic items will build up a skin dose of metal that is sufficient to elicit contact dermatitis, as explained by Midander et al. [3]. This becomes particularly important for nickel, since so many items in our daily life contain nickel. Well-known examples of such items that may give rise to nickel dermatitis are coins, keys, handles, eyelash curlers, tools, toys and scissors.

Metal release can be measured by immersing items in artificial sweat. Several studies have shown that when metallic items are submerged in artificial sweat, the initial release of metal ions is high. Already after 2 min, high concentrations can be detected in the sweat; for example, copper-nickel coins release nickel between 6 and 25 μg/cm^2/h and nickel-plated coins between 3 and 4 μg/cm^2/h; some dental alloys release cobalt between 1.5 and 4 μg/cm^2/h and chromium between 0.01 and 0.12 μg/cm^2/h, and hard metal discs released cobalt between 6 and 81 μg/cm^2/h. This is important for understanding why metals can be deposited on the skin after only short contact.

The total amount of a substance on the skin is important for developing allergy and reacting to an allergen [4]. This is true for metals as well as for other skin sensitizers. For metals, we often speak of the amount of ions per surface area (μg/cm^2). During the last years, several studies have shown that even a short and repeated contact with metals give rise to high doses of metal on skin. Jensen et al. [5] showed that nickel-allergic patients, performing their normal work tasks during 2 h, had skin doses of nickel varying between 0.05 and 0.3 μg/cm^2 on the volar aspect of the index finger. These patients had on-going vesicular hand eczema, which was significantly improved once the short and frequent occupational exposure had been reduced. At the 3-month follow-up, no eczema was present on the hands of the six patients. This study illustrates that even low doses of nickel on the skin can maintain hand eczema. Occupational exposure and any brief and repeated "private" exposure to metals must always be considered when seeing the patients at the clinic.

11.4 Source of and Exposure to Metals

Sources of metal exposure are present all around us in our daily life. This is particularly true for nickel, which is present in several items, for example, keys, coins, handles, tools, mobile phones, computers, jewellery, belts, buttons and cutlery, that we use every day and therefore are very difficult to avoid [6]. Exposure to nickel through food is most notably found in whole grain products, beans and lentils and from storing acidic food in stainless steel containers. Also dental braces may release

some nickel. Consumer exposure to chromium may occur through leather items such as shoes, belts, gloves, bags and wrist bands. Consumer exposure to cobalt is often considered to be rare, but some items such as computers and mobile phones may contain cobalt at the surface and some high fashion jewellery, cosmetics and even in leather as pigment. Cobalt and chromium are also used in dental alloys as well as palladium and gold. Hence, dental restorations may serve as an exposure to these metals. Also hip implants are often made of cobalt/chromium alloys, which may become a problem for the individual [6].

Occupational exposure to metals is common. Nickel was historically a male allergy in the plating industry. Occupational groups with high exposure to nickel are electroplaters, metal workers, hair dressers, carpenters, cashiers, etc. Occupational exposure to chromium takes place in the construction industry (although it has declined due to the EU limitation of chromium in cement), among tannery workers, electroplaters, dental technicians, welders and metal workers [7]. Cobalt exposure is prominent in hard metal workers, metal workers, construction workers, pottery workers and dental technicians [8]. Few occupational groups are exposed to palladium, most notably jewellers, dental technicians and electroplaters. Occupational gold exposure mainly occurs for electronics workers and jewellers.

11.5 When to Suspect Metal Allergy: Clinical Signs

Regarding consumers, the classic clinical picture for a dermatologist to suspect metal allergy is when the patients present eczema underneath a metallic item that has been worn for a long time, for example, jewellery, spectacles, watches or buttons. But also hand and foot dermatitis should be evaluated for metal allergy. This can be related to nickel, chromium and cobalt exposure. The prevalence of metal allergies is summarised in Table 11.1. Nickel allergy is still the most common allergy both among dermatitis patients and the general population.

11.5.1 Nickel

Occupational nickel dermatitis is often presented as chronic hand eczema. Nickel dermatitis in consumers is often explained by prolonged contact with different personal nickel-releasing items. However, it must be stressed that also consumers develop hand eczema by repetitive contact with a broad range of nickel-releasing items in everyday life (Table 11.2).

11.5.2 Chromium

Patients often have a persistent eczema, sometimes widespread. It can sometimes be missed due to the fact that it resembles atopic dermatitis, due to a marked dryness

Table 11.1 Examples of recent prevalence (%) of allergy to nickel, cobalt, chromium and palladium among dermatitis patients and the general population in Europe and North America (generally adults if not otherwise stated)

Metal	Country/region, period	Dermatitis patients				General population				Ref.
		n	W	M	Total	n	W	M	Total	
Ni	Europe, 1985–2010[a]	180,390	17–32	3–10	12–25					[11]
	Europe 2005–2006	19,793			19–24					[12]
	Denmark 1990/2006					3,460	9	1	5.9	[13]
	Denmark, 1995–1996[b]					1,146	13.7	2.5	8.6	[14]
	Spain, 2000–2005	1,092	26	3	29.3					[15]
	North America, 2009–2010	4,294			15.5					[16]
Co	Europe 2005–2006	19,793			6.2–8.8					[12]
	Denmark 1990/2006					3,460	0.4	0.1	0.2	[13]
	Denmark, 1995–1996[b]					1,146	1.5	0.6	1.0	[14]
	Sweden	3,790	7	9						[17]
	North America, 2009–2010	4,303			6.2					[16]
	Spain 2000–2005	1,092	8.3	2.4	10.8					[15]
Cr	Denmark 1985–2007	16,228	2.5	2.4	2.5					[18]
	Denmark 1990/2006					3,460	0.3	0	0.1	[13]
	Europe 2005–2006	19,793			4.5–5.9					[12]
	Denmark, 1995–1996[b]					1,146	0.2	1.0	0.5	[14]
	North America 2009–2010	4,306			2.3					[16]
	Spain 2000–2005	1,092	4.1	3.4	7.5					[15]
Pd	Spain 2000–2005	1,092	10.5	1.2	11.7					[15]
	Italy 1991–2000	4,446	6.7	2.3	5.3					[19]
	Italy 2006	3,093			13					[20]

[a]Patch test years: Denmark 1985–2010; Italy 1997–2010; Germany 1995–2010; UK 2002–2010
[b]Adolescents 12–16 years

and lichenification. Cement eczema is often initially displayed at the dorsal aspect of the hands, in a nummular pattern. It can in a later stage also involve the rest of the hand. Foot dermatitis is also common due to chromium in leather shoes or boots; hand eczema due to leather gloves and other leather items in contact with the hands is also seen.

Table 11.2 Examples of sources of exposures for consumers and occupational workers

	Sources of exposure – examples	
Metal	Consumer items	Occupational groups
Ni	Belts, buttons, coins, doorknobs, handles, jewellery, keys, laptops, mobile phones, sewing materials, tools, watches	Carpenters, cashiers, dental technicians, electricians, hair dressers, plating industry workers, metal workers, tailors
Co	Body implants, dental implants, jewellery (to some extent), paints, putties	Dental technicians, hard metal workers, metal workers, painters, pottery workers, printing industry
Cr	Cement, dental implants, galvanised metal items, leather items (belts, boots, gloves, shoes, wrist bands)	Construction workers, dental technicians, tannery workers
Pd	Dental implants, jewellery	Analytical chemists, electroplating workers, jewellers
Au	Dental materials, intracoronary stents	Electronics workers, jewellers

11.5.3 Cobalt

It is rare to find cobalt allergy without either nickel and/or chromium allergy in patients. The most prominent finding of solitary cobalt allergy reactions is found among hard metal, glass and pottery workers. It is often difficult for dermatologists to explain the sources of skin exposure to cobalt, because relatively little is known about the uses of cobalt.

11.5.4 Palladium

Regarding palladium allergy, it is rare to find it isolated, due to cross-reactivity with nickel, but concomitant sensitivity or contamination of patch test substances with palladium chloride has also been proposed. Contact stomatitis and oral lichen in patients with dental restorations and granuloma in pierced patients have been attributed to palladium allergy. Palladium allergy among dermatitis patients is often neglected, due to difficulties to find palladium exposure and the cross-reactivity with nickel.

11.5.5 Gold

Gold allergy is still a controversy among scientists and dermatologists. Skin contact with elemental gold has seldom been shown to cause allergic contact dermatitis. However, there are studies indicating that positive patch test results from gold sodium thiosulfate are increasing rapidly, but the clinical relevance of the findings is often not understood. Dental gold and intracoronary stents are of importance for gold sensitization.

11.6 How to Test and Pitfalls in Testing

In Table 11.3 the most common patch test concentrations are summarised and also which regions/countries that uses them. Several countries also have their own patch test series.

11.6.1 Nickel

5 % nickel sulfate in pet is the preferred patch test substance and is part of the European baseline series. 2.5 % is used in the North American baseline series, but this concentration is known to miss cases of nickel allergy.

11.6.2 Chromium

0.5 % potassium dichromate in pet is the preferred patch test substance and is part of the European baseline series. It is known that this concentration will give rise to some irritant reactions, but if using lower concentration, it is also easy to miss allergic patients. When lower concentrations are used, for example, 0.25 % as in the North American base series, fewer irritant reactions are seen but will also miss cases.

Table 11.3 Common patch test systems and concentrations.

Metal	Patch test system	Concentration	Baseline series
Ni	Finn Chamber or other chamber	Nickel sulfate 5 % pet	European
	Finn Chamber or other chamber	Nickel sulfate 2.5 % pet	North American
	T.R.U.E. TEST®	Nickel sulfate 0.2 mg/cm^2	
Co	Finn Chamber or other chamber	Cobalt chloride 1 % pet	European
	Finn Chamber or other chamber	Cobalt chloride 1 % pet	North American
	T.R.U.E. TEST®	Cobalt chloride 0.02 mg/cm^2	
Cr	Finn Chamber or other chamber	Potassium dichromate 0.5 pet	European
	Finn Chamber or other chamber	Potassium dichromate 0.25 pet	North American
	T.R.U.E. TEST®	Potassium dichromate 0.023 mg/cm^2	
Pd	Finn Cambers or other chambers	Palladium chloride 1 % pet	Not in baseline series
Au	Finn Chambers or other chambers	Gold sodium thiosulfate 2 %	Not in baseline series
	T.R.U.E. TEST®	Gold sodium thiosulfate 0.075 mg/cm^2	

11.6.3 Cobalt

1 % cobalt chloride in pet is the preferred patch test substance and is part of the European baseline series. It has been described that 1 % cobalt chloride may cause some false-positive reactions, sometimes described as porous reactions.

11.6.4 Palladium

1 % palladium chloride in pet is usually used to patch test patients. However, within research, there is a discussion about missing cases due to patch testing with the wrong salt for palladium. It has been suggested that by patch testing with sodium tetrachloropalladate might give a higher sensitivity to finding palladium-allergic patients, without the problem of cross-reactivity with nickel [9].

11.6.5 Gold

2 % gold sodium thiosulfate in pet is used for research studies. It is not included in the baseline series of Europe or North America. Although in the extended North America 80 Comprehensive Series and the T.R.U.E. TEST, gold sodium thiosulphate is included. When patch testing with gold compounds, a reading after 1 week must be included, since the reaction occurs late.

11.6.6 Other Test Methods

Contact dermatitis clinics and researchers sometimes patch test with serial dilutions of the metals to assess how sensitive the patient is. This is however not recommended for routine use. For nickel, the ability of the test to diagnose contact allergy is reproducible, while the strength of the patch test reaction may vary over time [10]. Patch testing with metal discs of different metal alloys is also performed in research to investigate the ability of different materials to cause dermatitis [1].

11.7 What to Tell the Patient if They Have a Positive Test

The most important thing is to avoid skin contact with items that can release the metal. Use spot tests (nickel and cobalt) as a quick screening tool for evaluating release (see below). For chromium, be careful with leather products, if possible chose vegetable-tanned leather (although not always safe), and avoid skin contact with wet cement and cement products. If the dermatitis in a nickel-allergic patient is persistent, although skin contact has been significantly reduced, it may benefit the patient to reduce oral nickel intake.

Remember that these metals are often used in coatings on items to give a shiny or mate surface, for example, computers and mobile phones. Sometimes the coating will wear off with using the item. So a computer or phone that was initially spot test positive may not be positive after some time has elapsed.

Regarding gold, tell the patient not to have a gold stent if a coronary operation is planned.

11.8 Quick Screen for Metal Release

To live with a contact allergy to nickel or cobalt can be made easier with the help of spot tests. Spot tests are solutions of chemicals that can be used to quickly evaluate if ions of a specific metal are released from items. The nickel spot test, also known as the dimethylglyoxime (DMG) test based on dimethylglyoxime and ammonia, has been used in dermatology since decades to identify nickel-releasing items. Different tests are commercially available. Using a drop of the test on a white cotton wool tip stick and then rubbing against an item will give a bright pink colour if nickel ions are released from the item. The test procedure takes 1 min (Fig. 11.1). In a similar way, the cobalt spot test will change colour from yellow to orange/red if cobalt ions are released from the item (Fig. 11.2). It is important not to use the two spot tests on the same surface since this might lead to misinterpretations of the colour change.

The DMG test has been validated and found to be highly specific. It correlates well to the nickel limitation in the EU legislation (0.5 μg/cm^2/week, Table 11.4). The DMG test has also been described in a CEN report as a screening test to indicate compliance with the nickel regulation.

To screen for chromium VI, one can use a solution of diphenylcarbazide. The reaction is based on a reduction of chromium VI to chromium III, illustrated by a bright purple colour. The test can be performed by placing an item in a white plastic

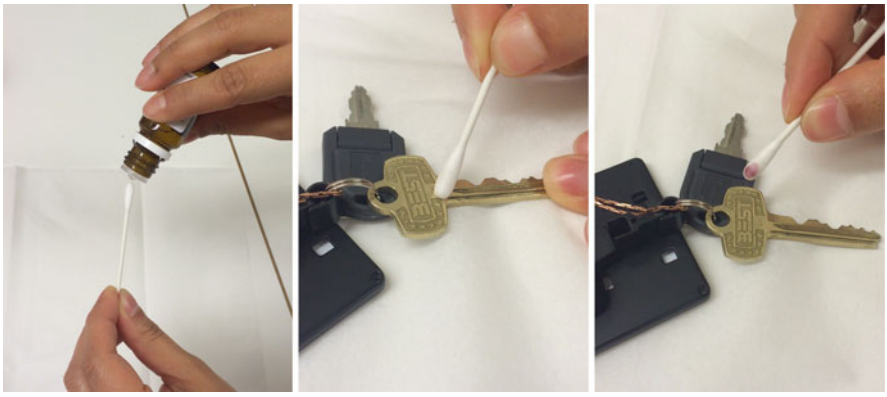

Fig. 11.1 Demonstration of the nickel spot test (dimethylglyoxime test). Put a drop of the solution on a white tipped cotton wool stick, and then rub against the item for 30 s; finally, read the result. A *pink* colour indicates that nickel ions are released from the item (key)

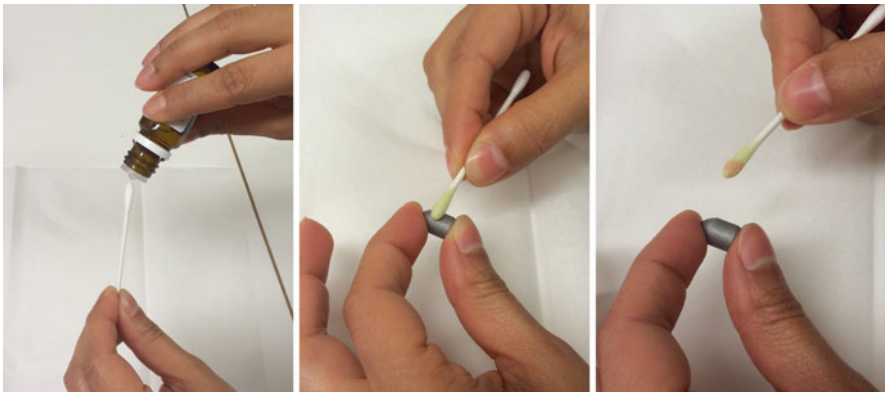

Fig. 11.2 Similar procedure as for nickel but with the cobalt spot test, where the solution is yellow before rubbing the item. An *orange*/*red* colour indicates that cobalt ions are released from the item (hard metal drill bit insert)

Table 11.4 Current legislation regarding nickel and chromium VI within the European Union

Metal	Limit value	Areas of use	Regulation and reference
Ni	0.2 µg/cm^2/week	Assemblies for pierced ears and other pierced parts	REACH; Commission Regulation (EC) No. 552/2009 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0552&from=EN)
Ni	0.5 µg/cm^2/week	Articles intended for direct and prolonged contact with skin Defined as: *Prolonged contact with the skin to articles releasing 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*The requirement shall be met for at least 2 years of normal use of the article	REACH; Commission Regulation (EC) No. 552/2009 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0552&from=EN) Q&A:s Unique ID 0935 (www.echa.europa.eu)
Ni	Nickel and nickel compounds are prohibited as ingredient in cosmetic products	All cosmetic products intended for human use	Regulation on cosmetic products (Annex II); Commission regulation (EC) No 1223/2009 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF)
Cr VI	2 mg/kg (0.0002 %)	Soluble chromium VI in cement	REACH; Commission Regulation (EC) No. 552/2009 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0552&from=EN)

Table 11.4 (continued)

Metal	Limit value	Areas of use	Regulation and reference
CrVI	3 mg/kg (0.0003 % by weight)	Leather articles or articles containing leather coming in contact with skin	REACH; Commission Regulation (EC) No 301/2014 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0301&from=EN)

REACH Registration, Evaluation, Authorisation and Restriction of Chemicals

container or in a test tube and dripping one to five drops of the solution onto the item. The colour change to reddish purple should be present after 1–2 min. It is important to have a blank sample to compare with, that means just the test solution in the same container, but with no item to react with. If iron is present in an item, chromium VI may react with the iron, and no colour change will occur; hence, you will receive a false-negative answer.

When using spot tests, another colour than the anticipated one may occur. For example, the DMG test may react with iron and give a reddish colour; the cobalt spot test may sometime show a green or blue colour, unknown which metals do this. Or sometimes the tip of the cotton wool stick will have a greyish/black colour on the test area. This discolouration will make it difficult to evaluate the spot test result. You cannot say that the test is either positive or negative. Such spot tests should be considered doubtful.

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