The Epidemiology of Contact Allergy to Metals in the General Population: Prevalence and New Evidences

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Abstract: Aluminium, Au, Be, Co, Cr, Cu, Hg, Ir, Ni, Pd, Pt, Rh and Ti represent causes of metal-induced allergic contact dermatitis (ACD) which expresses in a broad spectrum of cutaneous adverse manifestations. The exposure is primarily by skin contact with various items and products such as jewellery and piercing, cosmetics and tattoos, detergents, body implants and dental prostheses. To reduce the growth of the metal ACD among people, the European Union issued directives that limit the total Ni content in jewellery alloys and ban metals in cosmetics. Despite these regulations, the diffusion of metal ACD remained quite high. On this basis, a review of the epidemiological evidence of the metal-induced ACD is reported discussing the sources, the prevalence and the prescriptions.

Keywords: Allergic contact dermatitis, epidemiology, metals, metal contact allergy.

1. INTRODUCTION

Metals are ubiquitous in the environment; they are normally present in the Earth's crusts, in food and water. Today, metals are involved in several fields such as in industrial productions and in consumer products like for example jewellery, cosmetics, dyes, leather, dental/body implants and household products where they can be present as main components or as contaminants. It is for their numerous appliance fields that metals and their salts (Ni, chromate and Hg are examples) are able to cause the allergic contact dermatitis (ACD). In Europe, the Ni, Cr and Co ACD prevalence rates are of *ca.* 20%, 4% and 7%, respectively [1]. These data are similar to those evidenced in the USA with a prevalence of about 14% for Ni, 4% for Cr and 9% for Co [2, 3]. Females are affected by Ni and Co ACD more than males due to ear piercings and jewellery; while Cr ACD affects mainly males because of occupational exposure [4]. Moreover, it has been demonstrated that the incidence of Ni and Co ACD is higher at younger age, while the prevalence of Cr ACD remained high for the whole life [5]. In addition, other elements such as Al, Au, Be, Cu, Ir, Pd, Pt, Rh and Ti are of growing interest for their capability to act as allergens, even if the reason why these metals are able to create sensitization or the pattern of multiple metal reactivity are still not totally clear [4].

The ACD is characterized by a broad spectrum of skin symptoms ranging from dryness, chapping and inflammation to eczema and blisters. Discomfort is caused by skin inflammation and itching [6]. There are usually social stigmas present due to the discolourations and eruptions of local areas of the skin that are visible to others. For this reason, the importance of the ACD is not only related to the high number of affected people, but also to psychological - worsening of the quality of life of patients - and economical - increase expenses of each national health service - issues. In the USA, the cost for treating the ACD is more than 1 billion of dollar annually [7, 8], and people with ACD of the face and hands and, in some cases obliged to change their job, reported the worst life quality [9].

Nowadays, in the European Union (EU) are existing regulations for limiting metals in products destined for skin contact. In particular, the Council Directive 94/27/EC and the more restrictive Commission Directive 2004/96/EC limited the total Ni content in alloys, and the Council Directive 76/768/EEC (implemented by the Commission Directive 2004/93/EC) banned certain metals in cosmetic formulations [10-13]. However, more efforts should be undertaken to reduce and prevent metal ACD. Understanding the potency and prevalence of sensitizers, developing new diagnostic tests and informing about skincare strategies such as hygiene, gloves and protective creams can represent key points for the management of the risk to metal ACD [14]. In this context, this paper reviewed the epidemiological state-of-the-art on the sensitization and contact dermatitis caused by the skin contact with Al, Au, Be, Co, Cr, Cu, Hg, Ir, Ni, Pd, Pt, Rh and Ti contained in daily used products and items. The sources, prevalence rates and the prescriptions to avoid contact are discussed.

2. MOST REPORTED ALLERGENS

Nickel

Nickel is present in consumer products such as detergents, cosmetics, coins, jewellery, buttons, zippers, eyeglasses, buckles, clasps, inks, dental prosthesis, cookies and so on [4]. In consideration of its ubiquity, Ni allergy is the most prevalent of the metal allergies all over the world. In 2004, the ESSCA working group collected data from 31 dermatological departments in 11 European Countries (Austria, Denmark, Germany, Italy, Lithuania, Poland, Spain, Switzerland, Sweden, The Netherlands and United Kingdom) and reported positive responses to Ni in the 20.1% of

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the 10,000 patch tested subjects. In this study, Ni ranked at the first place among the allergens, the lowest percentage of Ni allergy being found in Denmark (9.7%) and the highest in Italy (32.2%) [1]. Similar results were obtained in other studies performed in different countries of the world. In fact, in Australia, Czech Republic, Hong Kong, India, Iran, Israel, Norway, Singapore, Turkey and USA the incidence was well above the 10-20% [3, 15-21]. In addition, patients who reacted to Ni were more likely to be females; a mean value of 25.1% of females were positive to path test against the 7.4% among males [15-21]. This was due to the growing popularity of ear piercing in combination with the use of imitation jewellery. Moreover, the same works reported that the prevalence of Ni allergy decreased with the increasing of age, probably because of a decrease in exposure to Ni contained in that objects. The EU recognized the possibility to regulate the presence of Ni in metallic objects destined to the contact with the human skin. The so-called "Ni Directive" and its more restrictive amendment were issued with the aim to prevent sensitisation to Ni (primary prevention) and to prevent exacerbation of ACD in pre-sensitized subjects (secondary prevention). The Directive limits the total content of Ni in metallic objects in direct and prolonged contact with the skin at no more than the 0.05% and, in addition, the same objects with the skin shall not release more than 0.5 μg/cm^2/week of Ni in sweat [10, 11]. At present, the effectiveness of the regulatory limit in reducing metal ACD is under debate. In fact, if on the one hand a decrease in Ni allergy after the Directive implementation was observed in two population groups passing from 24.8% to 9.2% and from 36.7% to 25.8%, respectively [22, 23], on the other hand, a study revealed a similar percentage (about 50%) of subjects sensitised to Ni before and after the Directive [24]. These last Authors evidenced that the Ni released in artificial sweat from cheap earrings available on the Italian market was over the regulatory limit from 10 to 450 times, posing a serious risk in the development of sensitization. Another factor able to pose a risk in the development of Ni ACD is represented by the relatively high presence of this metal in the Euro coins. This is the case of Italy where the Ni present in the Euro is much higher than in the old national current Lira arising the percentage of sensitised people [25].

Moreover, despite the EU has banned the use of Ni and Ni salts in cosmetic products [12, 13], cases of skin contact with Ni from cosmetics do exist. Sainio *et al*. determined total Ni in 88 different eye shadows and 51 products contained Ni above the safe allergizing limit of 5 μg/g and other 27 had Ni ranging 1-5 μg/g. These levels are far to provoke systemic toxicological effects, but they are able to generate risk of ACD in pre-sensitized people [26]. Kang and Lee quantified Ni in 7 out 15 henna tattoo mixtures in the range 2.94-3.96 μg/g. These levels are thought to generate sensitisation giving a contribution to the ACD occurrence [27]. Moreover, in 11 body creams sold as "Ni-tested" the highest amount of found Ni was 153 ng/g, but these levels were well below the threshold for sensitization [28].

Another route of sensitisation is represented by the Ni present in orthodontic devices such as wires, braces, bridges, crowns or amalgams. The continuative contact with saliva, the particular pH of the oral cavity, the temperature of the environment or also the friction of the metallic parts can cause the release of the metal. In this context, 15 patients with lichenoid oral manifestations showed positive reactions when patch tested and the positivity to Ni represented the 12.9% of all positive reactions. The substitution of the fixed replacements of white metal and crowns and dental bridges improved the healing of the disease [29]. Moreover, an Israelian study involved 121 patients with face and oral manifestations due to contact to dental materials. The frequent symptoms were related to cheilitis, perioral dermatitis, burning mouth syndrome (BMS), lichenoid reaction and orofacial granulomatosis and Ni one of the most common allergens with the 13.2% of cases [30]. Similar results was observed in a recent American study where patients suffering from different oral diseases reported positive reactions to Ni patch test equal to the 12.5% [31]. Interesting studies in adolescent population (Danish and Finnish) showed that the application of dental braces prior to ear piercing was associated with a significantly reduced prevalence of Ni allergy [32, 33]. Finally, it has been reported that the adoption of particular alloys (stainless steel, Ni-Ti or Ti alone and gold plated) or materials (ceramic or polycarbonate) in the production of dental devices can significantly reduce the release of Ni and the oral symptoms [34].

Nickel can also come from household consumer products; actually, its presence is related to the development of hand eczema in women. For this reason, in 1993, it was recommended that the amount of Ni in household products should not exceed 5 μg/g to avoid elicitation; in 2003, the limit was revisited and lowered to 1 μg/g [35]. This concentration limit allowed the decrease of the Ni content in this kind of products. In fact, in 1987, an Italian study reported a Ni mean value of 9.20 μg/g in 34 liquid or powder detergents with a percentage of sensitised people equal to 21% [36]. After the regulation, two studies reported Ni at level below 1 μg/g in 50 and 95 detergents [37, 38].

New causes of Ni allergy are related to activities as the use of cellular phone and the playing violin and trumpet. Patients showed erythema and papule in the hemilateral and preauricular region due to the handling of the phone and resulted positive to patch testing with nickel sulphate. In addition, the presence of free Ni on the surface of the phone was confirmed by the dimethyglyoxime test. The covering of the phone with a plastic case resolved the lesions [39-42]. A violinist revealed a reaction to Ni contained in the violin string; the substitution of the string was not the adequate solution because the tone of the string was significantly different form the original decreasing the quality of the sound [43]. A musician revealed scaling and crusting cheilitis on the lips. This condition was due to the presence of Ni in the mouthpiece of his trumpet. In this case the release of Ni was favoured by the contact of body fluids such as saliva and sweat; the use of the gold mouthpiece favoured the healing of the lip eczema [44].

Nickel allergies are also associated with metal button and snaps on blue jeans. In this context, Suneja *et al.* evidenced the presence of Ni in button of new and preworn blue jeans with the dimethyglioxime test. Authors highlighted that the presence of Ni was greater in new jeans than in preworn ones. In addition, they reported that one clear coat nail polish applied on the Ni containing button can prevent the metal release through two wash/dry cycles in a test environment [45]. In conclusion, mandatory labelling of jewellery, cloth-

ing, cosmetic or household products (e.g., "Ni free" or "hypoallergenic") could perhaps increase public awareness and possibly protect future consumers from Ni sensitisation.

Chromium

Skin contact with Cr and Cr-compounds occurs by alloys, cement, leather tanning, chemicals, anticorrosives, ceramic, wood preservatives, paints and varnishes, textile mordants and dyes, batteries, magnetic tapes, detergents and bleaches, electroplating and so on [4]. Variation in toxicity is associated with Cr(III) and Cr(VI); the former has a percutaneous permeability poorer than that of Cr(VI) resulting, thus, less able to elicit ACD [46].

In the European general population, the Cr allergy rate was approximately 4.5% in 2004, and both the lowest and the highest values were recorded in UK with 1.3% in Sheffield and 9.1% in Liverpool, respectively [1]. In Singapore and Turkey, the rate was similar (i.e., 5%) where the main sources of exposure were cement and tanned leather [21, 47]. Allergy in India has reached 10% and the cause was referable to the use of shoes without socks [48]. In most cases, the Cr allergy was more frequent in males than females. For example, in Czech Republic, percentages equal to 5.93% in males *vs* 2.81% in females were found and in Hong Kong 7.1% *vs* 2.3%; while in Turkey, the males were affected 2.3 times more than women, and in USA, this ratio was about 2 times in favour of males [15, 17, 21, 49].

The Cr(VI) is responsible for leather-induced dermatitis. In this regards, a Danish investigation on the content of Cr(VI) in 15 tanned leathers evidenced a concentration in the range 4.1-16.9 mg/kg and 5 patients had positive skin reactions after leather contact. Considering that no correlation between eczema and Cr(VI) or Cr(III) alone in leather was observed, it was suspected that skin responses were the result of a combined Cr(III) and Cr(VI) allergy [50]. In India, there were 155 cases of footwear dermatitis where the frequency of positive patch tests to chromate was the 45.8% [51]. The treatment to convert Cr(VI) in Cr(III) by soaking the tanned leather in 5% Vitamin C solution might minimize contact dermatitis [52].

As for Ni, allergy to Cr may be related to daily activities such as the use of cellular phone and playing guitar. In the first case, this problem was caused by the chromate present in the plating procedure of the phone [53], and, in the second case, by the presence of Cr in the guitar strings [54]. Moreover, Cr has been found in 88 different eyeshadows (9 of them contained soluble Cr above 2 μg/g) and in 11 moisturizing body creams (2 of them contained total Cr at 150 ng/g and 300 ng/g) [26, 28]. Also cheap earrings available on the Italian market released Cr in artificial sweat, with the highest value equal to 0.253 $\mu g/cm^2$/week [24].

Chromium contained in detergents and bleaches can increase the risk of ACD on the hand and forearm of women. In Italy, 8.4% of 65 cases resulted to be sensitized to total Cr contained in detergents at a mean concentration of 4.12 μg/g [36]. Household products marketed in Israel had very high total Cr concentration (i.e. above 5 μg/g in 56% of products) and the labelling of these products with regard to active ingredients was insufficient in most cases [55]. Basketter *et al*. recommended that household products should contain Cr(VI) < 5 μg/g or for a better protection < 1 μg/g in order to render the elicitation of chromium related ACD highly improbable [35].

Cobalt

Sources of Co include ceramics, enamels, paints as drying agent, catalysts, dental prosthesis, jewellery, particular adhesives, household products, hair dyes, fertilizers and feeding for animal [4]. In 2004, the ESSCA working group reports positive responses to Co in the 6.74% of the 10,000 patch tested subjects and Co is addressed as the third most important allergen. The lowest percentage of Co allergy is found in Denmark (1.1%) and the highest in Italy (17.6%) [1]. These rates are similar to those of other countries for the general population (i.e., the range reported is 5-10%); moreover, Co dermatitis was mainly prevalent in females than in males due to the wearing of jewels or personal adornments and patient's age did not significantly change the distribution of Co positive reactions [20, 21, 49, 56, 57].

Hand eczema due to cobalt salts in those responsible for domestic work has been observed [58]. A recent survey of 95 detergents and household cleaning products by the Dutch authorities showed that approximately 90% contained < 1 μg/g of Co, and all were just below 5 μg/g. In those products, the highest level of Co was 0.28 μg/g [37].

The release of Co in artificial sweat from a necklace caused the development of vesicular eczema; the chain released a concentration of Co 40,000 times higher than the minimal elicitation concentration dose. On normal skin, the minimum eliciting concentration was 2.26 μg/ml [59]. Cobalt contained in the alloy replaced Ni with the aim of being in compliance with statutory requirements of the Directive 94/27/EC. Even so, the modification of the alloy resulted to be unsafe [60]. Moreover, a Co-containing alloy for jewels was developed and tested on the cobalt allergic patients and 18% of them were found to be positive after 7-8 days of exposure [61]. Bocca *et al*. reported a release rate of Co ions in the range 0.013-0.188 $\mu g/cm^2$/week from the 40% of cheap earrings tested. These amounts are not likely to pose a risk for skin sensitisation [24].

In the last years, tattooing and ear piercing practices increased the incidence of Co-induced ACD among the juvenile population. A Swedish study performed on 520 young men demonstrated that the 1% of them had cobalt ACD related to ear piercing and there was a higher prevalence of sensitization in patients with pierced earlobes [62]. In Japan, 9 out of 106 pierced subjects had eczema and resulted to be positive to Co patch test, even if they did not significantly differ from non-pierced Co allergic patients [63]. Skin hypersensitivity caused by the presence of Co in the blue ink used for tattoo was observed. In particular, the tattooed patient suffered from urticaria on the tattooed right deltoid [64]. Kang *et al*. found Co in 4 different henna dyes at a concentration of about 3 mg/kg and they concluded that this amount can be able to provoke sensitisation but not contract dermatitis [27]. In addition, Co was determined in 88 colors of different brand of eye shadows, and *ca.* the 75% of the products contained more than the safe limit of 1 μg/g of Co. Although these amounts were low when systemic toxicological effects were considered, the Author's opinion was that the risk of acquire allergy in unsensitized subjects due to the use of these products cannot be excluded [26]. In a series

of 11 body cream labelled as "Ni tested", Co was quantified in 9 of them and it was below 5 ng/g, while in 2 cases, arrived at a concentration of 200 ng/g [28].

Clothing and shoes can be sources of Co-based ACD. In particular, a nurse with pruritic rush on the inner thighs and posterior calves resulted to be positive to Co due to the dyes used for manufacturing the blue trousers of the uniform [65]. Another nurse working in an intensive care unit reported itchy dermatitis on the dorsum of both feet and toes due to Co contained in the green plastic shoes [66]. In both cases, symptoms disappeared when the person stop to wear trousers and shoes. In India, the incidence of footwear dermatitis was 24.2% and the occurrence for Co sensitization was the 38.1%. This outcome was traced back to the habit of wearing shoes without socks [51].

Another cause of skin sensitisation is related to the presence of Co in polyester resins or in acrylonitrilebutadienestyrene (ABS) plastic. A cobalt catalyst, namely the cobalt naphthenate, was used in the production of plastic for PC mouse manufacture posing a risk for adverse skin reactions [67]. A patient presented a glove-associated hand eczema; in this case, the cobalt octoate was used as accelerator in the polyester resin production. The patient presented a significant improvement in his hand eczema by using cotton lined PVC gloves [68].

Mercury

Primary routes of exposure to inorganic Hg are dental amalgams and some preservatives that still contain Hg as a component like for instance the thiomersal [69]. Generally the skin rashes in the oral, head and neck area, itching, swollen lips, localized eczema-like lesions in the oral cavity symptoms due to the amalgams resolved on their own without treatment. In serious cases, instead, the replacement of the Hg-amalgams with others in resin or porcelain become mandatory to improve the disease in patients with patch test positive to Hg [70]. In addition, Hg containing dental fillings are considered to be the starting point for the development of oral lichen planus [71], orofacial granulomatosis [72] and the BMS [73] in Hg sensitized subjects. Thiomersal may be found in topical medications (ophthalmic and nasal preparations), cosmetics and vaccines. Thiomersal resulted to be the fifth most common allergen in patients with a positive patch test and it was found to be "possibly relevant" in 7.8% of those patients tested, with a single patient having "probable relevance" [74].

The use of skin whitening products is popular in developing countries and can cause Hg poisoning. People from Taiwan reported complications such as facial dermatitis and eczema; the two most detected allergens were Ni and Ammoniated Mercury (AM), and the majority of AM-sensitive cases resulted from cosmetics [75]. The association between the use of skin lightening creams and urinary or blood Hg has been reported in 314 cream users and the symptomatic Hg poisoning appeared at a concentration of Hg higher than 57,000 μg/g [76]. In Indonesia, a woman with membranous nephropathy habitually applied a Hg-containing skin whitening cream; testing showed her blood and urinary Hg levels higher than normal and the clinical signs subsided when she stopped using the cream [77]. A case report showed, in a 25-year-old woman, an itchy erythematous bullous dermatitis in the area of application of a Taiwanese whitening cream (i.e. the region around the eyes and mouth). The Hg concentration in cosmetic resulted to be the 7.2% w/w, and patch testing was positive to both mercury chloride and AM [78].

Tattoos, piercing and items made in polyvinyl chloride (PVC) can potentially be a hidden source of Hg sensitization. Metal salts that make up tattoo dyes can be responsible for allergic reactions. In particular, red pigments in tattoos may include the red isomer of mercury(II) sulfide (vermillion, cinnabar) and are known to produce a delayed hypersensitivity reaction [79]. Mercury together with Cr and Co have also initiated different types of skin reaction in tattooed areas [80]. The number of positive reactions was more than doubled among patients with pierced ear lobes than in those with un-pierced ears [81]. Patients with baboon syndrome and Au dermatitis due to ear-lobe piercing were tested with 0.05% mercuric chloride applied for 2 days; 5 of 5 patients with baboon syndrome were patch-test positive, 21 out 35 of those had pierced ears [63]. Mercury contained in PVC boots allowed the development of a severe ACD with exanthema in legs, groins and lateral parts of the trunk in a 5 year-old child affected by mercurochrome intolerance. Patch test revealed positivity to organic and inorganic Hg [82].

3. EMERGING ALLERGENS

Gold

In 1998–2000, Au ranked as the sixth most frequent cause of positive patch test reactions [83]. In Sweden, the 8.6% of 832 patients with suspected contact allergy on routine patch testing gave a positive response with gold sodium thiosulfate (GST). Other patients with contact allergy to GST also gave positive reactions to potassium dicyanoaurate, but were negative to gold sodium thiomalate (GSTM) and metallic Au [84]. In United Kingdom, the 4.6% of 278 patients had positive reactions to GST on routine testing [85]. All of these patients were females, with a mean age of 37 years and the most frequent site of eczema was the head and neck. In Japan, the 8.4% of 653 patients tested from 1990 to 2001 showed a positive reaction to gold chloride, and also in this work significantly more women than men reacted [86].

Only recently studies have realized that a more mundane use of Au in the form of the diverse alloys used in jewellery could bring to sensitization problems. Dissolution of metallic Au is notoriously difficult, but the process is facilitated by the presence of other metals in the alloy or in the neighbourhood [87, 88]. Gold allergy often presents as dermatitis at the site of jewellery contact, i.e., earlobes and fingers, but it also may present solely as eyelid dermatitis [89]. More positive reactions to 0.2% gold chloride in the patients with pierced than in patients without pierced ears have been documented [63]. In 1988, Fowler reported 2 women with eyelid dermatitis and positive patch tests to Au whose eruptions cleared with avoidance of Au jewellery. It was postulated that the allergen was being transferred from the hands to the eyelids as is commonly seen with allergic reactions to tosylamide formaldehyde resin [90]. In Portugal, contact allergy to GST and to potassium dicyanoaurate was found in 23 patients, all the reactors were women and had their ears pierced with Au earrings [91]. Ehrlich and Belsito found that 7 of 15 Au-allergic patients cleared their dermatitis by not wearing Au jewellery [92]. In Spain it was described that a lady pre-

sented Au-related ACD in the proximal root of a finger due to her wedding ring [93].

The presence of Au in metallic form has been visualized in human skin biopsies taken from areas of prolonged contact with the metal such as rings and jewellery, confirming absorption of the solubilized metal even through the intact stratum corneum [87]. In some cases, hypersensitivity to Au was associated with the formation of intracutaneous nodules in the earlobes at the sites of piercing. The nodules at pierced sites were described as lymphocytoma cutis, indicating the formation of a benign lymphocytic infiltrate, which is distinguishable from malignant lymphoma. When this did not resolve over time, nodules had to be removed surgically [94, 95].

Platinum Group Elements (PGEs)

The platinum group elements (PGEs) - platinum (Pt), palladium (Pd), rhodium (Rh) and iridium (Ir) - are rare in the earth's crust in comparison with other elements, but their specific physical and chemical properties have led to the development of some highly sophisticated technical applications, especially in the field of catalysis. The skin contact with PGEs is mainly *via* dental restorations and jewellery. A case of contact dermatitis from wearing a Pt ring has been reported [96]. Palladium is increasingly used in industry, jewellery and dentistry since the European Directive restricted the use of Ni. For this reason, during a 10-year period, the trend of sensitization to Pd in a clinic population increased to a maximum of 9.7% in the year 2000, with a higher percentage in females than in males. In the majority of cases, subjects were polysensitized (92.8%), but 7.2% of subjects were positive to Pd alone. Of Pd-sensitized patients, 40.5% complained of hand dermatitis, 47.4% of body dermatitis, and 1.7% of BMS [97]. In the study of Kanerva *et al.*, 7% of 700 schoolchildren had an allergic patch test reaction to palladium chloride [98]. Two cases of sarcoidal-type allergic contact granuloma due to Pd in ear piercing have been presented; the first to Pd only, and the second to Pd in combination to other metals [99]. Moreover, a case of developed dermatitis at contact sites of metallic spectacle frames which were declared as 99.7% Ti but with Au-plating using Au (90%), Cu (3%) and Pd (7%) has been observed [100]. In addition, Pd in dental restorations was the cause of oral symptoms such as stomatitis, mucositis and oral lichen planus [101-105]. Other works reported presence of swelling of the lips and cheeks, dizziness, asthma and chronic urticaria and most of them improved with the replacement of a metal-free dental devices [106-108].

Rhodium and Ir are sometimes reported as sensitizers in the form of salts, though not as metals, in subjects employed in precious metals or jewellery industries [109, 110] or with dental amalgams or prostheses [111, 112]. During 2001-2002, 720 consecutive informed eczematous patients were patch tested with 1% rhodium chloride and 1% iridium chloride, both in water. None of the 720 patch tested subjects showed positive or irritant reactions to iridium chloride, but 2 were found to have a positive patch test to rhodium chloride as well as other metals. These study results suggested that Rh and, above all, Ir are allergologically safe even in patients sensitized to metals [113].

As regards prevention strategies, since PGEs-containing dental or jewellery alloys have been identified as a possible source of sensitization, protection of the public from related adverse effects may be achieved either by limiting the use of certain alloys or by the use of alloys with high corrosion stability and thus minimal release of PGEs.

4. RARE ALLERGENS

Aluminium, Beryllium, Copper, Titanium

Contact sensitivity to Al is rare. Sensitization occurs during the frequent use of Al-containing antiperspirants or by aluminium adjuvants in vaccines and pollen extracts. Two types of reaction pattern are known: persistent granuloma at the injection site and recurrent eczema [114]. In Sweden, a patient who habitually apply an aluminium chloride roll-on antiperspirant developed an itchy dermatitis in the axillae and patch tests with aluminium chloride were positive [115]. Another case of axillary eczema was observed in a 16-year-old girl [116]. In addition, when Al is complexed with Zr and glycine in antiperspirants cutaneous granuloma and skin sensitivity have been observed [117]. Other two cases of contact allergy to Al after the use of topical medications containing aluminium acetotartrate were also reported [118]. Pruritus due to allergic conditions was seen after the usage of a toothpaste containing 30-40% of aluminium oxide. The replacement of the incriminated toothpaste with a brand free of Al resolved the pruritus in 1 month [119].

Only one case of contact urticaria to Al was recognized because of the presence of Al in Norwegian coins; the metal was present as a contaminant at the concentration of 0.01% at maximum. The test on patient showed erythema and itching after 5 min; a vesicular infiltration appeared after 8 min, and large crusts 2 days later [120]. Researchers have suggested that tattoo pigments containing Al can induce granulomatous reactions. In fact, in the 87% of 30 tattoo inks tested, the most commonly identified element was Al [121]. A case study of a 21-year-old man with delayed hypersensitivity granuloma formation in a tattoo has been reported. Four weeks after tattooing, three separate tumorous areas appeared in the violet areas of the tattoo. Intermittently pruritic lesions had existed for 5 months from the first examination [122].

The main sources of Be exposure are from the environment (i.e. the combustion of fossil fuel) or from corrosion of dental metal alloys. The exposure to salts of Be, such as fluoride, chloride, nitrate and sulphate, outcomes in local toxicity responses that can include 5 groups of cutaneous disease: ACD, irritant contact dermatitis, chemical ulcers, ulcerating granulomas and allergic dermal granulomas [123]. When Be-containing casting alloys are used for dental prostheses, skin and oral contact with Be can not be overlooked [124]. In this context, containing Be oral restorations provoked gingivitis in 2 subjects and the cause was also confirmed by the positive reactions to beryllium sulphate (1% in petrolatum) patch test [125], while other 3 patients showed positive responses to beryllium chloride (l% petrolatum) [126].

Copper is largely used in coins, jewellery, personal adornments (clasps, pins, belt, necklaces, buttons, hooks, etc.), dental restorations (oral prosthesis, bridges, band, wires

or cements) and intrauterine devices (IUDs). Copper salts are also used in agriculture as algicides and fungicides [4]. Copper has a low sensitizing power and, thus, it is a rare reason of ACD growth. The most reported clinical symptoms of ACD are related to the use of dental prosthesis and Cu-containing IUDs. Wöhrl *et al*. suggested that a high percentage (15.2%) of children sensitized to Cu was because of the increased use of this metal in dental amalgam [127]. In the same way, a woman developed ACD of the oral mucosa caused by the long-term exposure to Cu enriched dental amalgam fillings [128]. A relationship between intraoral metal ACD (i.e., mucositis) and pathogenesis of squamous cell carcinoma was observed by Hougeir *et al*., and, as a consequence of these findings, Cu was considered an additional risk factor in the evolution of cancer [129]. Additionally, a woman showed lesions of oral lichen planus due to the Cu contained in her prosthesis and the removal of the prosthesis made the lesions improved [130]. A bingo-hall worker's developed ACD caused by the presence of Cu in the 2-Euro coins and a woman was affected by ACD due to the Cu container in the composition of a microphone used in an ambulatory [131, 132]. A woman wearing a IUD reported skin eruption some day before menstrual cycle and the severity improved with the onset of the bleeding [133]. In another case, a patient showed diffused urticaria, angioedema of the eyelids and the labia majora and minora [134]. In both cases, the IUD users positively reacted to copper sulphate and removal of the IUD led to the disappearance of clinical signs. It has been reported that sensitization is achieved by combination of Cu and Ni ions. In 30 patients, the severity of patch test reaction to a Cu/Ni mixture was greater than to Ni alone, suggesting that Cu ions enhanced the sensitivity reaction to Ni [135]. According to the possible Cu-Ni cross-sensitization, it is risky to cover Ni goods with a layer of Cu to protect individuals allergic to Ni [127].

Titanium and its alloys are used for medical appliances like osteosynthesis, arthroplasty, pacemaker encasing, teeth and arch-wires, or in daily-use articles like body piercing and spectacle frames. The relationship between Ti and ACD is still under debate due to the lacking of adequate patch test preparations. Two cases of women wearing Au-pierced earrings reported lymphocytoma cutis; zinc was detected by scanning electron microscopy-energy dispersive X-ray spectroscopy (SEM-EDX) microanalysis from the specimen of case 1 and Au and Ti from case 2. This study demonstrated the existence of metal fragments in the lesion, which may suggest the permanence of metal for 20 years [136]. Moreover, a 68-year-old man who had pierced his ears approximately 10-years earlier developed nodules at the sites of piercings. Microscopic examination demonstrated epithelialized tracts surrounded by a granulomatous infiltrate of macrophages, lymphocytes, and plasma cells; a closer examination revealed minute brown-black particles within macrophages and SEM-EDX microanalysis demonstrated the particles to be composed of Ti, Al and V [137]. Contact dermatitis from topical exposure to Ti compounds is uncommon. In one report, patients presented an adverse reaction to titanium lactate used in a deodorant [138]; another paper observed generalized eczema in a patient working with melted Ti in a confined space [139]. Nanoparticles of titanium dioxide are added to various paints and tattoo pigments as a brightening agent; Ti is also a common ingredient in sunscreens as a physical blocker of UV light. In a recent study, a commercially available blue ink contained a high concentration of Ti (36.82%) [140].

CONCLUSIONS

Millions of people worldwide are affected by ACD. Different immunological responses can develop and be so severe to impact the working ability and to worsen the whole quality of patient's life. Metals are considered a major risk factor in ACD development; Ni, Co and Cr are the allergens with the highest occurrence while Al, Au, Be, Cu, Hg, PGEs and Ti are emerging. The items containing metals are jewellery, ear piercing, personal adornments (clasps, belts, pins, buttons), coins, dental restorations, body prosthesis, inks and tattoos, household products, hair dyes and leather tanning. In daily life people come in contact with the above and, thus, can be at risk of sensitization. Every contact with the allergen should be avoided to prevent the development of metal ACD in sensitized people; if this is not possible, personal care is suggested like for instance the use of cotton gloves or active and protective creams. Adequate warnings to costumer through products labelling and improvements, in terms of composition and/or plating, in industrial productions of alloys may be other possible ways of prevention. Even though some EU regulations have been issued to protect consumer's health, a high number of subjects still suffer metal-induced ACD. For this reason, further research should be done to identify the sources of the exposure to metal sensitizers, to characterize metal allergological strength and to develop new diagnostic *in vivo* and *in vitro* methods. The activity in this field should give support to create a common base of knowledge on this important health problem and to adopt successful prevention programs.

ABBREVIATIONS

ABS	=	Acrylonitrilebutadiene styrene
ACD	=	Allergic contact dermatitis
AM	=	Ammoniated mercury
BMS	=	Burning mouth syndrome
ESSCA	=	The European Surveillance System of Contact Allergies
EU	=	European Union
GST	=	Gold sodium thiosulfate
GSTM	=	Gold sodium thiomalate
IUDs	=	Intrauterine devices
PGEs	=	Platinum group elements
PVC	=	Poly(vinyl chloride)
SEM-EDX	=	Scanning electron microscopy – energy dispersive X-ray spectroscopy

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