

REVIEW

Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment

Malin G. Ahlström¹  | Jacob P. Thyssen^{1,2}  | Michael Wennervaldt¹  |
Torkil Menné¹ | Jeanne D. Johansen¹

¹National Allergy Research Centre,
Department of Dermatology and Allergy,
Herlev and Gentofte Hospital, University of
Copenhagen, Hellerup, Denmark

²Department of Dermatology and Allergy,
Herlev and Gentofte Hospital, University of
Copenhagen, Hellerup, Denmark

Correspondence

Dr Malin G. Ahlström, National Allergy
Research Centre, Department of Dermatology
and Allergy, Herlev and Gentofte Hospital,
University of Copenhagen, DK-2900 Hellerup,
Denmark.

Email: malin.glindvad.ahlstroem.01@regionh.dk

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Abstract

Nickel is the most frequent cause of contact allergy worldwide and has been studied extensively. This clinical review provides an updated overview of the epidemiology, exposure sources, methods for exposure quantification, skin deposition and penetration, immunology, diagnosis, thresholds for sensitization and elicitation, clinical pictures, prevention, and treatment. The implementation of a nickel regulation in Europe led to a decrease in the prevalence of nickel allergy, and changes in the clinical picture and disease severity. Nevertheless, the prevalences of nickel allergy in the European general population are approximately 8% to 19% in adults and 8% to 10% in children and adolescents, with a strong female predominance. Well-known consumer items such as jewellery and metal in clothing are still the main causes of nickel allergy and dermatitis, although a wide range of items for both private and occupational use may cause dermatitis. Allergic nickel dermatitis may be localized to the nickel exposure site, be more widespread, or present as hand eczema. Today, efficient methods for exposure quantification exist, and new insights regarding associated risk factors and immunological mechanisms underlying the disease have been obtained. Nevertheless, questions remain in relation to the pathogenesis, the persistent high prevalence, and the treatment of severe cases.

KEYWORDS

allergic nickel dermatitis, clinical review, contact allergy, nickel

1 | INTRODUCTION

Nickel is a transition metal with the atomic number 28. It is the fifth most common element on earth, and occurs in nature mostly as oxides, sulfides, and silicates. Nickel is primarily used in stainless steel and other alloys; it is also used in its pure form in plating and nickel compounds. Nickel is widely used in a large variety of products, owing to its high ductility, resistance to oxidation and corrosion, high melting point, ferromagnetism, and low cost.¹ In fact, nickel skin contact is difficult to avoid in everyday life. This review article serves as an overview of the current knowledge of nickel

allergy and allergic nickel dermatitis from a dermatological perspective.

2 | EPIDEMIOLOGY OF NICKEL ALLERGY

Nickel is the leading contact allergen in most industrialized countries worldwide. In Europe, the prevalence of nickel allergy has declined in some countries following implementation of the EU Nickel Directive.² The prevalences are approximately 8% to 19% in adults³ and 8% to 10% in children and adolescents in the general population,⁴⁻⁷ with a strong predominance in women as compared with men (4-10 times)

and in girls as compared with boys.⁸ In dermatitis patients, the prevalence is higher (adults, 12%-25%; children, 5%-30%).⁹⁻¹³ Nickel allergy has been less investigated outside of Europe, although persistently high prevalences have been observed in Asia and North America.¹⁴⁻²⁰ A higher prevalence of nickel allergy in individuals with atopic dermatitis has been shown in some studies, whereas others have found negative associations.²¹⁻²⁷ Furthermore, there are contradictory results regarding the prevalence of nickel allergy in carriers of filaggrin loss-of-function mutations.^{28,29} For further details on the epidemiology of nickel allergy, see other reviews.^{2,30}

3 | SOURCES OF NICKEL EXPOSURE

Nickel is ubiquitous in our environment, and humans will inevitably continue to be exposed to nickel. Topical skin nickel exposure occurs from metallic items, household products, and cosmetics, whereas systemic exposure is possible from food, water, surgical implants, and dental materials. Sources of nickel allergy have shifted over time as a result of industrialization, changes in fashion, and implementation of regulations.

3.1 | Occupational

Allergic nickel dermatitis was identified as an occupational disease on the hands and forearms in male nickel platers in the late 19th century.³¹ In the 1950s, the disease shifted towards being more common in women and stemming from consumer items. The decrease in the occupational setting was a result of improved industrial hygiene and technical developments. Nevertheless, nickel exposure has continued to be a problem in some occupational groups. In Denmark, nickel-related hand eczema was the most common cause of permanent disability among dermatological diseases between 1970 and 1976.³² Today, occupational nickel allergy has primarily been described in the industrial setting, in construction workers, and in the service and healthcare sectors (Table 1).^{8,33,34} In accordance with this, nickel skin levels capable of eliciting allergic nickel dermatitis have been found on the hands following the performance of normal work tasks in individuals from several of these occupations.³⁵⁻³⁸ A great variety of occupational nickel exposures have been found, including from coolants and cutting fluids, work tools, keys, electrical components, coins, sewing needles, dental tools and alloys, crochet hooks, dermatoscopes, guitar strings, and computers.^{36,39-44} The relevance of nickel as an occupational allergen may, in some cases, be difficult to elucidate, because of simultaneous irritant exposure, or because of many short but repeated nickel exposures, possibly from various sources.

3.2 | Consumer

Stocking suspenders, jewellery, spectacle frames and watches were reported as causes of nickel allergy and dermatitis between the 1930s and 1960s.⁴⁵⁻⁴⁷ Stocking suspenders were reported to be especially problematic, leading to nickel allergy and widespread dermatitis.⁴⁶ In

TABLE 1 Examples of occupations associated with nickel allergy and dermatitis

Bar staff
Car mechanics
Carpenters
Cashiers
Caterers
Chefs and cooks
Cleaners
Construction workers
Electricians
Electronic assemblers
Metal workers
Nickel platers
Nurses
Retail clerks
Sale assistants

the 1970s, metallic buttons in blue jeans became the leading cause,^{48,49} and, from the 1980s, the increased use of earrings led to an epidemic of nickel allergy, which finally resulted in a regulation.⁵⁰⁻⁵²

Today, nickel is used in a wide range of metallic items, and may also been found in detergents and cosmetics. Nickel release that is capable of eliciting allergic nickel dermatitis has been reported from selected metallic items (Table 2).^{6,39,43,53-64} Only some of these items are listed in the current nickel regulation. Although the current main causes of nickel allergy and dermatitis are presumed to be well-known risk items such as earrings and jewellery,⁶⁵ the widespread use of nickel may be of importance for the continuing high prevalence of nickel allergy.⁶¹ Recent reports have shown that various metallic items intended for short but repeated skin contact can lead to accumulation of nickel on the skin over time.^{61,66-69} These exposures may not be as obvious and may therefore not be studied to the same extent, which is why little is known about their clinical implications. Knowledge of the importance of

TABLE 2 Examples of risk items (non-exhaustive list)

Category	Types of item	References
Jewellery	Earrings, hair clasps, finger rings, necklaces, bracelets	46,52
Metal on clothing	Buttons, zips	6,47,50,51
Toys	Key chains, dolls, toys	53,54
Coins	€1 and €2, various national coins	55,56
Tools	Files, pliers, saws, hammers, wrenches	57,58
Accessories	Belt buckles, bags, umbrellas	6,47,48
Utensils	Keys, needles, electronic cigarettes	48,49
Electronic devices	Laptop computers, mobile phones, activity bracelets	48
Other	Spectacle frames	59,60

nickel in cosmetics is less well studied. The safe limit in pigmented makeup products such as eye-shadows and mascaras has been estimated to be <5 ppm, although discrepant results exist regarding the clinical implications of such exposure.⁷⁰⁻⁷²

3.3 | Diet

Nickel occurs naturally in drinking water and in various foods, and is hard to avoid in our diet. Examples of nickel-rich foods include chocolate, legumes, shellfish, grains, nuts, and canned food.⁷³ Large variations are seen according to the nickel content of the soil where the food was produced. Furthermore, nickel release from cooking utensils may add to total nickel ingestion.⁷⁴⁻⁷⁶ Nickel allergy has not been described after nickel intake, but a flare-up of allergic nickel dermatitis⁷⁷ and the development or aggravation of vesicular hand eczema have been reported.^{78,79} It is estimated that a normal diet results in the ingestion of <300 µg of nickel per day.⁸⁰ Nickel is not regulated in food, but in drinking water a maximum of 20 µg/L is permitted in the EU.⁸⁰ The level of nickel in drinking water is approximately 1 to 10 µg/L.⁸¹ Water that contained 53 µg/L was reported to cause facial dermatitis in a Korean woman.⁸²

Jensen et al showed a dose-response relationship between nickel intake and dermatitis flare-up. In this double-blind study of nickel-allergic and healthy controls, a single dose of 0.3 or 1 mg of nickel sulfate resulted in dermatitis in 40% of nickel-allergic individuals, and a single dose of 4 mg resulted in dermatitis in 70% of nickel-allergic individuals, whereas none of the controls reacted. In nickel-allergic individuals, nickel intake of 4 mg caused statistically significant widespread dermatitis as compared with placebo.⁸³ In a later review of the existing literature, it was estimated that the nickel content in a normal diet (0.22-0.35 mg) may result in systemic dermatitis in 1% of nickel-allergic individuals, and a slightly higher exposure (0.55-0.89 mg) may result in systemic dermatitis in 10% of individuals.⁸¹

3.4 | Surgical implants

Metallic implants, for example, orthopaedic and cardiovascular, inserted into the human body may release nickel and other metal ions. Following insertion, the development or aggravation of vesicular hand eczema and dermatitis in the overlying skin have been described.⁷⁹ Dermatitis in nickel-allergic individuals resulting from the use of various surgical utensils and materials has been described.^{84,85} The prostheses used for hip replacement have changed over time. In the 1960s, they were made of metal-on-metal and had high rates of metal release; from the 1970s, metal-on-plastic models were used, which produced fewer wear particles.^{86,87} In the 1980s, more highly engineered metal-on-metal prostheses were reintroduced, but they are rarely used today, because of complications suffered by patients.⁸⁸

An association between metal allergy and an unfavourable outcome of an implant has been suggested, although the causation has not been outlined.⁸⁹ There are also contradictory results regarding a possible association between nickel allergy and coronary in-stent restenosis.^{90,91}

3.5 | Dental materials

Dental alloys made of stainless steel are widely used in brackets, headgear, and retention wires, and alloys made of nickel-chromium are widely used in dental prostheses.⁹² An association between metal allergic contact dermatitis and dental alloys was found in a large European study.⁹³ Even though the release of nickel from the same materials has been shown to be low,⁴² the corrosive effect of the oral environment is thought to increase nickel release.⁹² A protective effect of inserted dental braces prior to ear-piercing has been shown, which suggests induction of oral tolerance.^{94,95} Overall, studies in this area are sparse.

4 | EXPOSURE QUANTIFICATION

Quantification of nickel exposure may be performed by direct nickel measurement on the skin or by indirect estimation of nickel release from, or content in, a material. The amount of nickel release from the surface of a material has been directly linked to the risk of eliciting allergic nickel dermatitis,⁹⁶ whereas the nickel content is of less importance.⁹⁷ The proportion of nickel in the surface of a material or in fluids can be determined with X-ray fluorescence^{98,99} or, even better, with X-ray photoelectron spectroscopy.^{43,100}

4.1 | The dimethylglyoxime test

The dimethylglyoxime (DMG) test is a commercially available colorimetric spot test for screening of excessive nickel release from a metallic item. A cotton stick moistened with DMG test solution (containing DMG [1%], ethanol, and ammonia [9.9%]) is rubbed against the surface for up to 30 seconds, and, if the nickel release is >0.5 µg/cm² per week, it turns pink (Figure 1).¹⁰¹ The test has a sensitivity of 59% and a specificity of 97.5%.¹⁰² The sensitivity can be increased by



FIGURE 1 A positive dimethylglyoxime test reaction indicated by the pink colour of a cotton stick rubbed against a key

pretreatment of the items with artificial sweat and by heating.¹⁰³ The method has also been used to visualize nickel directly on the skin, for which the lowest limit of detection was $0.13 \mu\text{g}/\text{cm}^2$.¹⁰⁴

4.2 | Nickel release in artificial sweat

In the current standard reference test to show compliance with the nickel regulation (EN1811), the corrosive effect of sweat is utilized to estimate nickel release from a metallic item.⁹⁷ The material of interest is immersed in artificial sweat for 1 week, and subsequent nickel release into the solution is measured.¹⁰⁵ Limitations of the method include the difficulty in measuring complex surface areas of an item, the fact that it is time-consuming, and its high cost. Nickel release is initially high, and then decreases rapidly over time.^{43,68,106} Nickel release into blood plasma is approximately doubled as compared with release into artificial sweat.¹⁰⁷ Furthermore, differences between materials, and the importance of factors included in a touch, such as friction, are not included.⁶⁷ It has been suggested to include shorter time intervals than 1 week for measurement or to develop new, more accurate analyses.^{8,108}

4.3 | Skin sampling methods

Nickel skin exposure ($\mu\text{g}/\text{cm}^2$) has been measured in nails and in the skin with various types of wipe sampling, finger immersion, and tape stripping.^{35,109–115} Following sampling, the nickel content is analysed, for example, by inductively coupled plasma mass spectrometry. Measurements of nickel nail deposits in individuals with suspected occupational exposure to nickel was used in combination with elicitation thresholds to define occupational exposure with a cut-off value of $8 \mu\text{g}$ of nickel per gram.^{109,116,117} Finger immersion has been used to evaluate nickel skin exposure in different occupations.^{35,110} By the use of this method after coin handling, nickel skin contamination was found to be directly proportional to the duration of coin rubbing, although considerable interindividual variation existed.¹¹⁰ Acid wipe sampling has been used to measure the nickel skin surface dose with high accuracy in some occupations and in experimental studies (recovery of $>90\%$).^{36–38,67,111,118} A self-sampling method, based on the acid wipe technique, was recently developed.¹¹⁵ In the tape stripping method, the same skin area is stripped to quantify nickel deposition onto the skin surface, and stratum corneum (SC) penetration.^{112,119} This method has mostly been utilized to study nickel penetration after application of nickel salts and nickel powder,^{120,121} and, more recently, after metallic nickel exposure (Figure 2).¹¹² Punch biopsies may also be used to study permeation.^{122,123}

5 | NICKEL SKIN DEPOSITION

Nickel ions are transferred to the skin from contact with nickel-containing materials, household products, and cosmetics. Nickel deposited onto the skin may be shed by desquamation of keratinocytes, washed away, accumulate on/in the skin over time, or penetrate into the viable epidermis. The nickel skin dose ($\mu\text{g}/\text{cm}^2$) is

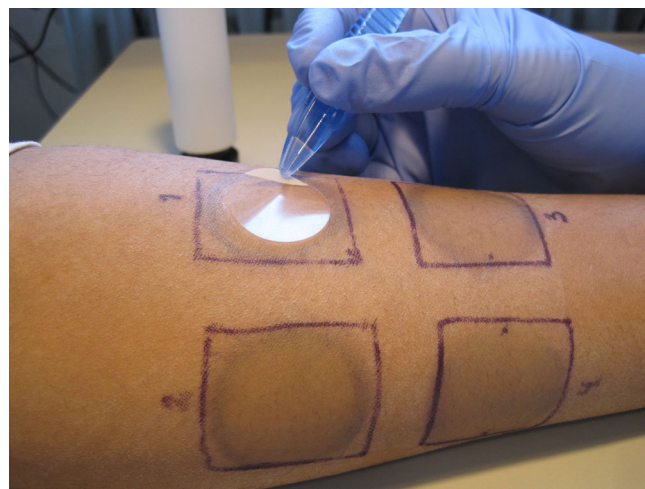


FIGURE 2 Tape stripping of four volar forearm skin areas exposed to metallic nickel discs

of major importance for the resulting penetration, and thereby the risk of allergy. In each specific situation, the resulting nickel skin dose is determined by external and local skin factors, such as the type of material, the condition of the skin, the amount and acidity of sweat, friction between the skin and the material, and the duration and number of skin contacts.^{43,67,108,124,125} Our understanding of this complex interplay is inadequate. Historically, prolonged metal-skin contact has been expected to be required for critical nickel skin deposition.⁹⁷ However, more recently, rapid skin deposition following contact has been shown to occur after seconds to minutes.^{67,108,110,112} Erfani et al found that $4.7 \mu\text{g}$ of nickel per cm^2 was deposited onto the fingertip following 3 seconds of contact with metallic nickel, and Ahlström et al showed nickel skin doses of 10.1 to $23.5 \mu\text{g}/\text{cm}^2$ after three 10-minute exposures.^{67,112} These studies underline the importance of friction for the resulting nickel skin deposition.^{100,108} Furthermore, major interindividual differences in nickel skin deposition seem to exist.^{67,108,110,112} Studies are needed to further elucidate the mechanism of skin deposition and the actual state of nickel on the skin (free nickel ion, bound to proteins, etc.).

6 | NICKEL SKIN PENETRATION

Nickel skin penetration (diffusion from the outer skin surface into the SC) and absorption (diffusion from the outer skin surface through the skin and eventually into the systemic circulation) has been studied in animal and human skin in vitro and in vivo.

The main barrier to nickel penetration is the SC, for which a lag time of 50 hours has been described.¹²⁶ Nickel has been shown to accumulate in the upper SC following exposure,^{112,120,121,123,127} which is why a possible cumulative effect of repeated or different exposure sources must be considered.¹²⁸ If it reaches the viable epidermis, nickel may cause contact allergy. Studies with mouse models have suggested that the trivalent, rather than the divalent, nickel ion may be the immunogenic form, and that oxidation occurs on inflamed

skin.¹²⁹ A paradox in the pathogenesis is the slow diffusion through the SC combined with the distinct allergenicity. From the existing literature, it seems that nickel may penetrate the SC through three routes: transcellular, intercellular, or appendageal.¹²¹ There is limited knowledge on the proportion of penetration through each route and the influence of various skin conditions. Water-soluble nickel salts (sulfate and chloride) are formed by oxidation of nickel by strong inorganic acids (eg, hydrochloric and nitric acid), and are mostly deposited in the outer SC.¹²⁰ Nickel is strongly chelated by histidine-rich filaggrin proteins, which are hypothesized to slow SC penetration.¹³⁰ Nickel may also react with sweat and form divalent nickel ions that can penetrate through all three routes.¹²⁰ Different degrees of lipophilic nickel soaps result from nickel reacting with weak organic acids (eg, octanoic and lauric acid), which may penetrate at a continuous rate through the intercellular route.^{121,131} Rapid appendageal diffusion (through hair follicles and sweat ducts) within minutes of exposure has been visualised, and is thought to be utilized by nickel ions paired with chloride or low molecular weight acids in sweat.^{121,122}

Barrier dysfunction caused by constitutional (eg, atopic dermatitis) or acquired (eg, irritant exposure) factors may augment metal skin absorption.^{132,133} Apart from the skin dose, the state of nickel being deposited onto the skin, and the skin barrier status, penetration is determined by the size of the exposure area, the anatomical site, skin thickness, the vehicle (or skin exudate/sweat), occlusion, temperature, sex, race, age, density of hair follicles and blood flow, humidity, and pH.^{121,126,134,135}

The amount of nickel absorption, the flux through the skin and the lag time (the time period from exposure to constant flux) have been studied *in vitro* by the use of Franz cells.^{123,136,137} In a review by Hostýnek, it was concluded that the permeability coefficient was difficult to use for nickel and other transition metals, and that only a first approximation of diffusivity could be provided by Fick's first law.¹³⁴ In the existing studies, the flux is in the range of 1 to 300 ng/cm² per hour, with a lag time of 6 to 15 hours, being highly determined by the size of the nickel particle and the skin barrier integrity.^{136,138} For example, the flux was increased 10-fold to 100-fold following prior needle abrasion as compared with normal skin.^{136,137}

7 | IMMUNOLOGY

Nickel contact allergy is a cell-mediated delayed-type hypersensitivity reaction (type IV) to nickel ions. During the sensitization and elicitation phase of the type IV reaction, both the innate and adaptive immune systems are activated in a complex way that has not yet been completely elucidated.¹³⁹ During sensitization, the nickel ion penetrates the skin and can bind directly to Toll-like receptor 4 (TLR4) on dendritic cells (DCs), leading to stimulation of the IKK2-nuclear factor- κ B cascade, among others. Innate immune signalling independent of TLR4 may also exist.¹⁴⁰ Activated DCs upregulate costimulatory molecules and migrate to the local lymph node, where nickel is presented to naive T cells by major histocompatibility complex (MHC) II molecules. If the DC activation is sufficient, allergen-specific T cells and

memory T cells proliferate and migrate to the blood and the skin, resulting in sensitization.¹⁴¹ In case of ineffective DC activation, proliferation occurs with a surplus of regulatory T cells, and tolerance is believed to occur.^{142,143}

During the elicitation phase, the clinical expression of allergic nickel dermatitis is initiated by re-entry of a nickel ion. The nickel ion is captured by the DC and presented to specific effector T cells by the MHC II complex. This leads to activation of skin-resident memory T cells and recruitment of memory T cells from the circulation through endothelial activation,¹⁴⁴ resulting in inflammation and cellular damage, visible as allergic nickel dermatitis.¹⁴⁵ As compared with other contact allergens, there is a difference in the way in which nickel and other metal ions are presented by the MHC II complex to the T cell receptor of CD4⁺ T cells. First, metal ions interact with nitrogen or oxygen in amino acid chains on the MHC II molecules and/or on the MHC II-bound peptides to produce non-covalent, reversible coordination protein-metal complexes.¹⁴⁶ Classic allergens, in contrast, form stable covalent bonds with MHC II-bound proteins. Second, several different molecular interactions between the metal ion, MHC II-peptide complex and T cell receptor may exist, including direct binding to the MHC II molecules, and cross-linking of the MHC II molecule and the T cell receptor independently of MHC II-associated peptides.¹⁴⁷ The mechanism of activation of CD8⁺ T cells by nickel and MHC I is not known, and the importance of CD8⁺ T cells in nickel allergy is debated.¹⁴⁸

Recently, skin-resident memory T cells have been harvested from skin with previous nickel dermatitis and a lowered elicitation threshold for nickel exposure. These cells have been shown to lead to a specific "local skin memory" for nickel, even though the immunological mechanisms are not fully elucidated.¹⁴⁹ Although new discoveries have been made in the field in recent years, there is still a lack of understanding of the immunological mechanisms underlying the disease. Nickel-induced antibody-mediated type I hypersensitivity has rarely been reported.^{150,151}

8 | TOLERANCE

Oral nickel exposure may lead to tolerance. In epidemiological studies, the prevalence of nickel allergy was lower in individuals who wore dental braces prior to ear-piercing than in those who underwent piercing first.^{94,95,152} In addition, Russian women who were exposed to nickel in drinking water had a lower prevalence of nickel allergy than non-exposed Norwegian women from a nearby geographical area, with the same prevalence of ear-piercing. This finding was suggested to be a result of the development of tolerance in the Russian women.¹⁵³ The immunological mechanisms of tolerance have been only partly elucidated. T helper CD4⁺ cells have been shown to proliferate following nickel stimulation in individuals without nickel allergy, as compared with both CD4⁺ and CD8⁺ upregulation in nickel-allergic individuals.¹⁵⁴ A subtype of CD4⁺ T cells, named T regulatory 1 cells, secreted interleukin (IL)-10 to a higher extent in non-allergic individuals than in allergic individuals, and this may inhibit the

maturation of DCs.¹⁴² Another subtype, CD4⁺ CD25⁺ T cells (T regulatory cells), has been isolated from the skin of non-allergic individuals.^{155,156}

9 | DIAGNOSING NICKEL ALLERGY

Nickel allergy is diagnosed by patch testing on the upper back, as indicated by clinical suspicion of allergic contact dermatitis.¹⁵⁷ Other methods, which have been used mainly for research purposes, are in vitro testing, for example, the macrophage migration test, the lymphocyte blast transformation test, and the lymphocyte transformation test,¹⁵⁸ the memory-lymphocyte immunostimulation assay,¹⁵⁹ and intradermal testing.¹⁶⁰

9.1 | Patch testing

Patch testing with 5% nickel sulfate (2.0 mg/cm²) in petrolatum is used in the European baseline series, whereas 2.5% (1.0 mg/cm²) is used in North America (Figure 3).^{19,157} Nickel sulfate is less irritant than nickel chloride,^{45,161} although nickel chloride more accurately resembles real-life exposure to nickel alloys in contact with human sweat.¹²⁶ In general, doubtful and irritant patch test reactions to nickel are less common than those to other metals, such as cobalt and chromium.¹⁶² Follicular reactions of the poral type have been described after nickel contact, but whether these reactions are irritant or allergic is unknown.^{161,163} Nevertheless, follicular spongiosis may be observed in early allergic, but not irritant, reactions.¹⁶⁴ A follicular reaction may also be a result of a low level of allergen exposure.¹⁶⁵

The reproducibility and relevance of a positive nickel patch test reaction are generally thought to be high,^{166,167} although weak reactions may disappear over time.¹⁶⁸ In contrast, when infants are tested, both irritant reactions, low reproducibility and low clinical relevance are generally described.¹⁶⁹⁻¹⁷¹ One good example is the high prevalence of nickel allergy in infants, for whom nickel exposure and allergy are expected to be very modest.¹⁷² However, in a recent study of patch tested children and adolescents with dermatitis, the relevance was found to be ~70%, with a low proportion of irritant reactions,



FIGURE 3 Positive patch test reaction (++) to nickel sulfate 5% pet. in an 8-mm Finn Chamber

and this was also seen in the youngest age group (1 to 4 years).¹⁷³ No difference in reactivity seems to exist between the right and left upper back when a high level of standardization of the patch test is achieved.¹⁷⁴ The recommended times for patch test reading are day (D) 2 and D3 or D4, and around D7.¹⁵⁷ One single reading on D2 was found to result in 18% to 29% less reactions than adding an extra reading on D4.¹⁷⁵

9.2 | Other tests

Serial dilution patch testing with nickel salts in different concentrations is used to determine the individual degree of sensitivity and to discriminate between allergic and irritant reactions. Repeated open application testing with nickel salts can be used to study the elicitation threshold after simulated use.¹²⁴

10 | THRESHOLDS FOR NICKEL ALLERGY

Nickel has been found to be a weak to moderate allergen in animal experiments,^{176,177} and a moderate allergen in humans,¹⁷⁸ which contrasts with the high prevalence of nickel allergy in the general population. Studies on nickel allergy have shown that various internal and external factors are important in the complex pathogenesis, and many questions remain.

10.1 | Sensitization

Regarding nickel sensitization, no threshold has been defined. No new studies on human nickel sensitization have been performed in the EU, as it is considered unethical to perform such studies according to EU regulations. Irritated or inflamed skin probably increases the risk of sensitization.^{176,179} In 1963, Vandenberg and Epstein induced nickel sensitization in 9% of 178 healthy volunteers with repeated occluded exposures to 25% nickel chloride in water with 0.1% sodium lauryl sulfate on briefly frozen skin.¹⁸⁰ Kligman described nickel sensitization in 12 of 25 healthy subjects who underwent an occluded patch test with 10% nickel sulfate on irritated skin.¹⁷⁸ Furthermore, Wall and Calnan observed that repeated exposure to 42 ppm nickel in an aqueous solution resulted in nickel sensitization in 7 of 16 operators in the electroforming industry.¹⁸¹ Ear-piercing with earrings releasing various nickel amounts (0.02-0.79 µg/cm² per week in distilled water) led to symptoms suggestive of nickel dermatitis in six of nine healthy subjects.¹⁸² Finally, Menné concluded that nickel alloys that are known to induce nickel sensitization released 10 to 100 times more nickel in artificial sweat than alloys that never or rarely cause sensitization.⁹⁶

10.2 | Elicitation

The thresholds for nickel elicitation have been more extensively studied. A correlation between the sensitization and elicitation area doses has been difficult to establish, although sensitization doses are

generally higher.^{176,183} Larsen and Brandrup found 100-fold to 1000-fold higher nickel release from buttons inducing sensitization than from buttons eliciting nickel dermatitis in nickel-allergic individuals.⁴⁹

Nickel allergy is a lifelong disease, but reactivity may vary over time. A 250-fold variation has been described for the same individual over time.¹⁸⁴ Similar variability in elicitation thresholds are found between individuals (250-fold).^{184,185} The differences in thresholds for groups of nickel-allergic patients are less pronounced than the considerable interindividual differences.¹⁸⁶ Fischer reviewed the literature on occluded nickel exposure, and found that 1% of nickel-allergic individuals reacted to 0.07 µg/cm², 5% reacted to 0.44 µg/cm², and 10% reacted to 1.04 µg/cm².¹⁸⁶ In the study that formed the basis for the Danish nickel regulation, the most sensitive nickel-allergic individuals reacted to stainless steel with an estimated nickel release corresponding to 0.01 µg/cm² per week.⁹⁶ In this study by Menné et al, 267 nickel-allergic individuals were patch tested with 15 nickel-containing alloys with known nickel release in artificial sweat over a period of 1 week.⁹⁶ Metallic discs that released >1 µg/cm² per week gave strong patch test reactions, whereas nickel release of <0.5 µg/cm² per week led to weak reactivity. Although there was one exception, it was concluded that the nickel allergy problem would be minimized if alloys released <0.5 µg/cm² per week.

10.3 | Factors determining the risk of nickel allergy and allergic nickel dermatitis

The accumulated nickel skin dose (µg/cm²) is recognized as the major factor that determines the risk of nickel allergy and allergic nickel dermatitis.^{124,187} The elicitation threshold for accumulated repeated nickel exposures corresponds to one higher single dose.¹⁸⁸ Other essential factors are the type of exposure (on skin, penetrating, or systemic), the skin status (intact, irritated or damaged), the skin area, the bioavailability in the skin, the duration, previous dermatitis, and combined exposure with irritants.

In general, the studied safe limit of metallic items placed onto the skin is higher than that for exposure from cosmetics.^{183,189} Furthermore, the sensitization and elicitation threshold for a skin-penetrating exposure (eg, piercing) is thought to be lower, including after healing of the skin.^{182,190} Tolerated systemic exposure (eg, nickel in food) differs,⁸¹ and there are regional differences in skin penetration.¹⁹¹

The risk of elicitation on skin with a defective barrier is generally increased, because of enhanced permeability, immunomodulatory effects, or a combination of these.^{137,192,193} Allenby and Basketter showed that the elicitation threshold of a 48-hour occluded patch test with nickel sulfate on inflamed skin was 0.0075 µg/cm²,¹⁹⁴ which was expected to be 100 to 1000 times below the threshold on normal skin.¹⁷⁹ Simultaneous irritant exposure can result in both additive, synergistic and agonistic interactions as compared with nickel exposure alone.^{161,195,196} The bioavailability of nickel in the skin is increased with occlusion,^{124,126,186} and an approximately 6-fold higher dose may be needed for elicitation with open exposure than for elicitation with occluded exposure.¹⁸⁶ Furthermore, the matrix affects

bioavailability, and this is increased by the use of nickel chloride as compared with nickel sulfate,¹²⁶ and with aqueous solutions as compared with pet.¹³⁵ The application of low nickel concentrations (15 µg/cm²) on a large area resulted in an increased potential for elicitation as compared with a smaller area.¹⁸⁷ Furthermore, in skin with previous allergic nickel dermatitis, a long-term allergen-specific local memory is present, leading to a lowered elicitation threshold.¹⁹⁷

It is generally thought that prolonged contact with nickel is required for elicitation, although there are only a few studies in this area. Nielsen et al showed a worsening of existing hand eczema in nickel-allergic individuals after finger exposure for 10 minutes daily to 10 ppm and then 100 ppm nickel over a 2-week period.¹²⁵ In a recent study, it was shown that three 10-minute exposures to metallic nickel discs led to elicitation of allergic nickel dermatitis in pre-irritated skin in 10 of 16 nickel-allergic individuals.⁶⁹ Also, it has been shown that relatively short and repeated occupational skin contact with nickel can lead to hand eczema in nickel-allergic individuals.^{36,198} Nickel probably builds up on or in the skin after repeated contact at the same skin site.

11 | CLINICAL PICTURE, INCLUDING HAND ECZEMA

Nickel-allergic individuals may develop allergic nickel dermatitis, which is the clinical disease. Allergic nickel dermatitis is usually present as a local reaction on the skin in direct contact with a metallic item, termed the "primary eruption" site.⁴⁶ The acute clinical manifestation of allergic nickel dermatitis is erythematous, oedematous skin with papules, vesicles, and oozing, whereas the chronic phase is characterized by dry, scaly and fissured skin. The most common anatomical localization for the primary eruption has shifted over time, owing to changes in exposure. Bonnevie was the first to describe dermatitis caused by stocking suspenders on the thighs (Figure 4A). Today, the disease is seen on the hands, face (earlobes), or body sites with direct skin contact (jewellery, buttons, etc) (Figure 5). In cases of a high level of nickel skin exposure, nickel may be absorbed transcutaneously and spread to secondary sites. These "secondary eruptions" are usually symmetrical, and involve flexural areas, the eyelids and the hands in form of vesicular eczema, or the entire body (generalized). In 1956, Calnan described secondary eruptions in 75% of patients with stocking suspender dermatitis.⁴⁶ Stocking suspenders and other consumer items were previously shown to result in generalized dermatitis (Figure 4C).^{45,46} In some parts of the world, generalized dermatitis is still common, as recently shown in North American paediatric patients aged ≤18 years.^{19,199}

It has generally been recognized that the threshold for elicitation of allergic nickel dermatitis at previous affected skin sites is lowered.²⁰⁰ Furthermore, a flare of dermatitis at sites of previous allergic nickel dermatitis has been shown both after systemic and after cutaneous nickel exposure at other sites (Figure 4B). More recently, a specific "local skin memory" has been described for nickel.¹⁴⁹ In addition to dermatitis flare-up, systemic nickel exposure may lead to

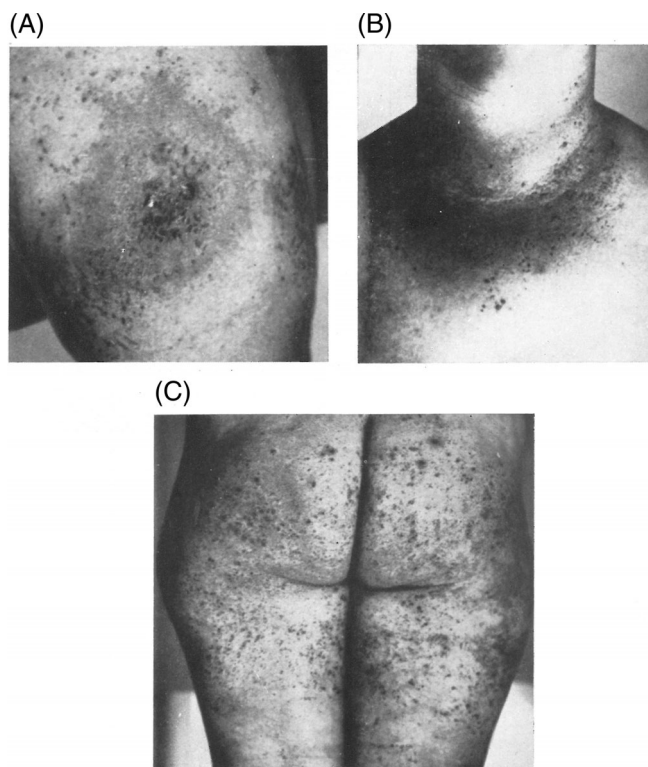


FIGURE 4 Allergic nickel dermatitis after wearing of suspenders (A) on the thigh as a primary eruption on the direct contact site, (B) around the neck, probably owing to flare of dermatitis caused by previous wearing of a necklace, and (C) generalized on the buttocks and thighs. Reprinted with permission from Gylendal³⁸



FIGURE 5 Allergic nickel dermatitis localized on the abdomen after use of a belt buckle

generalized dermatitis, vesicular hand eczema, flexural eczema, and the “baboon syndrome.”^{46,81,201,202}

Some studies have found an association between nickel allergy and loss-of-function mutations in the filaggrin gene. The pathogenic mechanism is thought to be decreased chelation of nickel in the SC, leading to more effective penetration.^{29,130}

Nickel-allergic individuals have an increased risk of developing allergic contact dermatitis on the hands, that is, hand eczema.²⁰³ Hand eczema may be caused by direct nickel exposure on the hands, and often occurs in the context of irritant contact dermatitis.^{125,181} High nickel exposure on the hands led to nickel allergy and hand eczema in workers in the plating industry.³¹ Moderate repeated nickel exposures

(10–100 ppm) aggravated existing hand eczema in nickel-allergic individuals in an experimental set-up.¹²⁵ It was recognized early that hand eczema is often present in nickel-allergic individuals despite no obvious direct exposure.⁴⁶ In these individuals, hand eczema was thought to be a secondary eruption after cutaneous exposure (eg, jewelry)^{204,205} or systemic exposure (eg, food and metal prostheses).⁸³ Methods developed later for exposure quantification showed nickel skin doses that were capable of eliciting hand eczema following short repeated skin contact with metal items such as coins.^{35,110} Moreover, individuals with hand eczema may have an increased risk of developing nickel allergy.⁷⁸

Hand eczema in nickel-allergic individuals is of the vesicular type and often becomes chronic and difficult to treat.^{206,207} Occupational nickel exposure often presents as chronic hand eczema. Elimination of the dermatitis-causing metallic item(s) improves the prognosis of hand eczema in nickel-allergic individuals,²⁰⁴ although job change may be required.²⁰⁸ The association between nickel allergy and hand eczema decreased in young Danish women of the general population following implementation of the EU Nickel Directive, indicating a better prognosis resulting from reduced nickel exposure.²⁰⁹

12 | CONCOMITANT METAL ALLERGIES

Nickel allergy may occur concomitantly with allergy to other metals. Concurrent nickel-cobalt and nickel-chromium allergy is thought to be a result of co-exposure to these metals from the same alloys or materials or by exposure to different materials,^{30,210} whereas immunological cross-reactivity may explain concomitant nickel-palladium allergy.²¹¹ Of 19 723 dermatitis patients, 11% had a solitary positive nickel patch test reaction, 2.32% reacted positively to nickel and cobalt, 0.65% reacted positively to nickel and chromium, and 0.56% reacted positively to all three metals.²⁴ A Spanish study of 1092 dermatitis patients found that ~40% of nickel-allergic individuals also had positive patch test reactions to palladium, whereas 97% of individuals who reacted positively to palladium also reacted positively to nickel.²¹² Concomitant cobalt or palladium allergy may be related to the nickel patch test reactivity.^{213,214} Importantly, patients with concomitant nickel and cobalt allergy often present with severe hand eczema with a poor prognosis.²¹⁵

13 | PREVENTION AND REGULATORY INTERVENTIONS

Exposure reduction aimed at preventing nickel allergy in the general population is possible through regulations, education and information campaigns to educate consumers and retailers, decontamination of exposed skin surfaces, the use of protective creams, or the use of protective gloves. Regarding the last of these, nickel may penetrate rubber gloves, although other materials, such as PVC, are protective.²¹⁶ Protective creams either prevent the allergenic effects of nickel (eg, by nickel chelation or oxidation) or inhibit nickel permeation of the SC. Barrier creams with chelating agents such as 5-chloro-

7-iodoquinolin-8-ol (clioquinol),²¹⁷ EDTA²¹⁸ or diethyldithiocarbamate (DDC)²¹⁹ have been used, with variable success.¹³¹ Surface plating of nickel-containing objects offers limited protection, as it may contain pores and cracks that may lead to nickel release when in contact with human sweat.^{47,220}

Regulations to prevent nickel allergy were introduced because of an epidemic of nickel allergy and dermatitis in young women caused by the increased use of jewellery and earrings in the 1980s. National regulations in Denmark (1989), Sweden (1990) and Germany (1991) preceded the EU Nickel Directive, which was adopted 1994, but first came into full force in 2001, owing to extensive lobbying by industries.²²¹ Outside of Europe, a regulation exists in China, but not in other countries such as the United States, Thailand, and Australia.

The EU Nickel Directive was based on the Swedish (part 1) and the Danish (part 2) nickel regulations, and originally prohibited: (1) nickel in post assemblies used during epithelialization of the piercing wound, unless they were homogenous and the nickel concentration was less than 0.05%, and (2) nickel release greater than 0.5 µg/cm² per week for items intended for direct and prolonged contact with the skin, such as jewellery, watches, and buttons.²²² The second category was restricted to a few listed items, and did not include items intended for temporary contact, for example, keys and coins, as such items were estimated to constitute a limited risk in the context of nickel allergy. Furthermore, items in the second category with a coating were required to fulfil the release limits for at least 2 years of normal use. Only one amendment of the limits of the EU Nickel Directive were made following the implementation.²²³ In 2005, the first category was changed to include all items inserted into pierced parts of the body (not only during epithelialization), and the limit was changed from nickel content to nickel release (<0.2 µg/cm² per week). The change was based on a report evaluating the safety of piercing post assemblies on limited scientific evidence.^{107,182,224}

Mobile phones were included in the regulation in 2009, following reports in the national media in Denmark that many mobile phones released excessive amounts of nickel.²²⁵ In the same year, the EU Nickel Directive was included in REACH, the EU Chemicals Regulation.

The effect of the EU Nickel Directive was studied in Sweden by the use of systematic market surveys of nickel release from various regulated consumer items. Three studies with comparable products bought before and after the implementation of the EU Nickel Directive showed an effect of the EU Nickel Directive. Twenty-five per cent of 725 items were DMG test-positive in 1999, 8% of 786 items in 2002 to 2003, and 9% of 659 items in 2010.^{63,226,227}

Over the years, the actual nickel release limit has fluctuated, owing to changes in the regulatory limits, the reference test methods used, and the interpretation of the analysed results.²²⁸ In particular, the implementation of an "adjustment factor" to compensate for methodological difficulties was criticized, as it allowed 10-fold higher release than set by the regulation.²²⁹ In the original EU Nickel Directive, the duration of "prolonged contact" with the skin was not further described. In 2014, the European Chemicals Agency (ECHA) defined "prolonged contact" as potentially more than 10 minutes on three or more occasions within a 2-week period, or 30 minutes on one or more

occasions within a 2-week period.¹²⁸ Subsequently, the ECHA proposed a list of examples of articles to be covered by the definition,²³⁰ but the work was discontinued because of divergence of views on the draft guideline (<https://echa.europa.eu/completed-activities-on-restriction>).

In cosmetics, nickel is forbidden in the EU, but it can be present as an impurity.²³¹ Toys are currently regulated by the EU Toy Directive, whereby the limits are 75 mg/kg from dry, brittle, powder-like or pliable toy material, 18.8 mg/kg from liquid or sticky toy material, and 930 mg/kg from scraped-off toy material.²³²

14 | TREATMENT

Early recognition of the disease and exposure limitation or avoidance improve the prognosis of nickel dermatitis.²⁰⁴ A thorough assessment of the patient's nickel exposures, both at the workplace and at home, is important. Recently, a standard operational procedure for evaluating the relevance of nickel occupational exposure in cases of hand eczema was suggested.²³³ Patient education about possible nickel sources and instruction in the use of the DMG test for items in direct skin contact is recommended to limit exposure.¹⁵⁷ The use of protective gloves can be effective in the industrial setting,²³⁴ although nickel may penetrate rubber gloves.²¹⁶

Allergic nickel dermatitis can be treated with topical corticosteroids or calcineurin inhibitors. Hand eczema in nickel-allergic individuals can be treatment-resistant, in particular in cases with a mixed aetiology with irritant or atopic components. Normally, treatment with potent topical corticosteroids is recommended, but, in more severe cases, systemic medication may be indicated.²³⁵ Historically, chelating agents administered orally such as disulfiram (Antabus), DDC and triethylenetetramine have been used, with limited success. This form of treatment is rarely used nowadays, owing to the risk of serious side-effects such as hepatotoxicity and only partial remission of dermatitis, with quick relapse following termination.²³⁶⁻²³⁸ The mechanism of action of disulfiram is thought to be mobilization of pre-existing nickel deposits, as transient increases in serum and urinary nickel levels and a flare of dermatitis are seen.²³⁹ Recently, experimental systemic treatment with anti-IL-17 led to a slight reduction in reactivity in nickel-allergic individuals, although no effect on inflammation was observed.²⁴⁰

Nickel desensitization with daily oral nickel intake for weeks to months has showed interesting results, with the development of partial tolerance.^{241,242} A low-nickel diet may improve symptoms in a subpopulation of nickel-allergic individuals.^{243,244} It must be stressed that this approach should be carefully considered in each case, and, if it is considered necessary, be performed in a controlled way, as the risk of malnutrition is considerable.

15 | CONCLUSION

Nickel allergy remains common and continues to be a health problem in the general population. Still today, nickel allergy may become

chronic. Clinicians should be aware of the potential chronicity of the disease, resulting in decreased quality of life and societal and economic impacts. Despite the extensive research in the field, many questions remain regarding the pathogenicity of nickel allergy, as effective treatment in the case of hand eczema is lacking.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ORCID

Malin G. Ahlström  <https://orcid.org/0000-0003-2092-7826>

Jacob P. Thyssen  <https://orcid.org/0000-0003-3770-1743>

Michael Wennervaldt  <https://orcid.org/0000-0001-5071-283X>

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