

NICKEL ALLERGIC CONTACT DERMATITIS

Nickel is one of the most common causes of allergic contact dermatitis (ACD). Nickel sensitization is the condition of being allergic to nickel. Nickel ACD reactions occur in nickel-sensitized (or nickel allergic) individuals. The reason for the relatively high prevalence of nickel sensitization is due to the use of nickel-releasing consumer items that come in direct and prolonged contact with the skin. Although exposure may occur through some occupational settings generally associated with soluble nickel salts, the marked prevalence of nickel sensitization in the general population is primarily due to consumer dermal exposure to nickel released from nickel metal in plated articles or some alloys (e.g., in jewelry, watches, eyeglasses). Nickel sensitization and nickel ACD require prolonged exposure of the immune system to nickel absorbed through the skin. Once sensitized, exposure to a sufficient amount of nickel over an extended time causes nickel ACD reactions by the immune system, called elicitation. The release of nickel ions is responsible for causing nickel sensitization and nickel ACD, which are threshold effects (requiring release of ions above a specific amount to cause a reaction). Alloys such as many stainless steels contain nickel but do not release a sufficient amount of nickel-ions to cause an individual to become nickel sensitized or have a nickel ACD reaction if they are already nickel-sensitized.

Exposure to nickel ions through inhalation and oral exposure has not been shown to induce nickel-sensitization in non-nickel-sensitized individuals. Rather, oral exposure in some cases has been demonstrated to reduce susceptibility or even result in immunotolerance to dermal nickel sensitization.

Legislation in the European Union has been put in place to decrease the consumer dermal exposure to nickel-releasing articles intended to come in direct and prolonged skin contact, to reduce the prevalence of nickel-sensitized individuals and the number of nickel ACD reactions in already nickel-sensitized individuals. Occupational exposure is being reduced through risk management measures within the workplaces. The nickel industry supports and encourages these practices to reduce and minimize nickel allergic contact dermatitis.



Nickel-releasing jewelry is a common cause of nickel allergic contact dermatitis.

1 INTRODUCTION

Many chemical agents, including nickel, can cause allergic contact dermatitis (ACD) which results in inflammation of areas of the skin in sensitized individuals. While nickel ACD can cause pain, inflammation and discomfort, it is not life threatening because it causes a delayed-type allergy (type 4), which cannot trigger anaphylactic shock like some other types of allergies (type 1, 2, or 3).

Elemental nickel and sweat-soluble nickel salts both cause ACD by solubilization of nickel substances and the formation of nickel ions, during intimate and prolonged contact with the skin and sweat. The rate of nickel ion release to the skin is dependent primarily on the specific substance having contact with the skin. Non-occupational exposure to nickel in Europe, primarily through jewelry in piercings (e.g., earrings) and direct and prolonged skin contact with nickel-releasing jewelry, clothing fasteners, etc. has reportedly sensitized from 12-15% of females and from 1-2% of males.

The nickel industry supports the intent of legislation such as the European Union's Nickel Directive (94/27/EC as amended), now subsumed into the REACH Regulation Annex XVII. This prohibits the use of nickel in products intended for direct and prolonged skin contact if this will result in solubilization of nickel at a rate exceeding 0.5 micrograms per square centimeter per week or in the case of body piercing, a lower rate of 0.2 micrograms per square centimeter per week (as measured by EN1811 testing). Furthermore, the nickel industry accepts the expert opinion of dermatologists who state that such a regulation is expected to reduce the prevalence of nickel sensitization incidence of nickel ACD in the general population to very low levels.

There is no justification for banning nickel from uses in general consumer products unless there is clear evidence, resulting from a detailed risk assessment, that such a use poses a significant health risk. The Danish EPA (Environmental Protection Agency) conducted a target risk assessment on nickel as used in euro coins.⁽¹⁾ The conclusion of this report for consumers was: "There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already." The use of nickel in coinage does not pose a health risk for the majority of the general population because this application does not involve direct and prolonged contact with the skin under normal handling and use. Many populations, including North Americans, that have used nickel in coinage for many decades show few cases of nickel ACD associated with coins.

The use of most stainless steel alloys in consumer products does not constitute a health risk for nickel ACD. This is because most stainless steels have not been demonstrated to cause nickel ACD in nickel-sensitized individuals, nor do they release sufficient amount of nickel ions. In addition, such items would not come into contact with the skin at the required intimacy or for the required time to cause nickel sensitization reactions.

The nickel industry will continue to be supportive of scientific research on the mechanism of nickel sensitization, improving tests for nickel sensitivity, and conducting studies to ensure that nickel-containing materials are used in appropriate applications.

While technical in nature, this is not a peer-reviewed science paper. It is intended to be an overview of a topic that has generated very extensive literature over a long time period.

2 WHAT IS ALLERGIC CONTACT DERMATITIS?

Many chemical agents such as poison ivy, rubber accelerators, epoxy resins, certain solvents, certain perfumes, and some metals and soluble salts of metals (*e.g.*, nickel, chromium, cobalt, gold, mercury) are able to cause ACD. A broad range of skin symptoms ranging from dryness, chapping, and inflammation to eczema and blisters characterizes this condition. Discomfort is caused by skin inflammation and itching.



Photo courtesy of Jere Mammino, DO

Nickel ACD from nickel releasing necklace clasp.

Nickel sensitization is not an inherited condition. It is related to intimate and prolonged skin contact (*i.e.*, exposure) by nickel-containing and releasing materials, nickel metal, or nickel soluble salts. Nickel ACD was first noticed in occupational settings where soluble forms of nickel came into contact with worker's skin. Individuals working in electroplating shops, in battery manufacturing, and with nickel catalysts were the most susceptible to exposure. Work related nickel dermatitis is now relatively rare due to preventative occupational hygiene measures.

Non-occupational nickel sensitization is well documented. It was first observed in individuals who had skin contact with clothing items releasing nickel, such as nickel-coated buckles, zippers, and clasps. The prevalence increased with the increasing use of nickel-plated jewelry. A common cause of nickel sensitization and nickel ACD is now body piercing, which may involve inserting nickel-releasing studs into the wound to prevent closure during healing. Once healed, with the stud removed, additional contact with nickel in the pierced area may occur by wearing jewelry or posts in piercings that release a significant amount of nickel ions.

3 WHAT ARE THE CONDITIONS NECESSARY FOR INDUCING NICKEL SENSITIZATION?

The development of nickel ACD requires that an individual become immunologically sensitized to nickel. This is termed the induction phase or sensitization phase and the length of this phase varies greatly between individuals. It can range from 1-3 weeks to develop, following days to weeks of intimate contact in a piercing or on the skin with a form of nickel that can release a sufficient amount of solubilized nickel ions onto the skin. The quantity of nickel ions that is sufficient to induce sensitivity varies with the individual. If the skin is already damaged, sensitization may be induced more quickly and by lower amounts of the solubilized nickel. Temperature, the presence of other allergic conditions, gender, and age may also be determining factors for 1) susceptibility, 2) the amount of nickel ions required for a reaction, and 3) the time

to develop sensitization to nickel. Induction of nickel sensitization most commonly originates from body piercing but is also more likely if skin exposure is combined with irritants and/or moist skin.

A nickel-sensitized individual, when re-exposed to nickel ions on the skin in sufficient amounts, may have an allergic response within a matter of hours. This is termed the elicitation phase, which often occurs at a lower concentration of nickel ions than required for inducing sensitization in the first place. The elicitation of nickel ACD usually occurs at the site of exposure but can occur in skin remote from the site of contact with nickel where previous nickel sensitization reactions have occurred.⁽²⁾

Whilst systemic elicitation of ACD in individuals sensitized by direct skin contact is well documented for a small proportion of nickel-sensitized individuals, there exists some controversy⁽³⁾ about the ability to sensitize individuals when nickel exposure is oral, intravenous, or inhaled. Only about 1-10% of dietary nickel is absorbed by the body. Average daily-ingested intake of nickel is about 200 micrograms. A few studies have shown that nickel-sensitive individuals orally given >5,000 micrograms nickel (as NiSO₄) as a single dose had a nickel ACD response. While such exposures are in excess of those encountered in normal diets, some researchers suggest that dietary control of nickel intake may help in the ongoing treatment of nickel ACD caused by other sources. These researchers have correctly identified foods high in nickel content (*e.g.*, nuts, chocolate, beans), but they have sometimes incorrectly advocated the avoidance of cutlery, bowls, etc. made from stainless steel, which do not release significant amounts of nickel.

A correlation between dermal nickel sensitization and asthma due to respiratory exposure to soluble nickel has not been demonstrated. This lack of association is likely the result of different immunological mechanisms of the two types of allergy. Respiratory sensitization is known to be a type 1 mediated immunological reaction, whereas skin sensitization involves a type 4 reaction.

4 WHAT PORTION OF THE POPULATION MAY BE AT RISK?

Studies of the prevalence of nickel sensitivity generally show that in the general population up to 15% of women and up to 2% of men are nickel sensitive.⁽⁴⁾

Public health advocates are using these figures to project that over 10% of the world's population, that is hundreds of millions of people, are at risk of being sensitized to nickel. This projection, however, fails to take into account the method of exposure that has likely caused the current prevalence. It is generally agreed among dermatologists that "the principal way in which sensitization can be induced in susceptible individuals appears to be by contact with a high concentration of sweat-soluble nickel from a localized area."⁽⁵⁾

Nickel-releasing ear-piercing studs, nickel-plated jewelry, and nickel-plated clothing clasps are viewed as the items primarily responsible for the current prevalence of nickel sensitivity. Body-piercing practices are increasing in North America and Europe. The significant differences in prevalence between females and males is sometimes correlated with the much higher prevalence of ear-piercing among women, particularly in European cultures, but other factors such as hormone differences and the tendency for young women to wear more and/or low quality jewelry than males may also play a role.⁽⁶⁾

An important question is: If the use of nickel-releasing materials in jewelry and ear-piercing studs were reduced, what would be the resulting long-term risk of nickel sensitization among the population? Regulatory controls (similar to the Nickel Directive and REACH) were adopted in certain Scandinavian countries towards the end of the last century and many reports have now demonstrated a significant reduction in the prevalence of individuals testing positive for nickel sensitization.⁽⁷⁻¹⁴⁾ The Nickel Directive has now been in place in Europe as a regulatory control since 1998 and more widespread support of the earlier Scandinavian studies of decreased sensitization to nickel in European countries has developed.

5 WHAT REGULATORY CONTROLS ARE CURRENTLY IN PLACE?

In 1991, Denmark banned the sale of nickel-releasing objects that contact the skin for prolonged times and which release approximately >0.5 micrograms/cm²/week as measured by a dimethylglyoxime (DMG) test.⁽¹⁵⁾

The amended Nickel Directive has now been subsumed into the REACH regulation (EC) Annex XVII.⁽¹⁶⁾ This says that nickel:

1. "Shall not be used:
 - a. in all post assemblies which are inserted into pierced ears and other pierced parts of the human body unless the rate of nickel release from such post assemblies is less than $0.2 \mu\text{g}/\text{cm}^2/\text{week}$ (migration limit);
 - b. in articles intended to come into direct and prolonged contact with the skin such as:
 - earrings,
 - necklaces, bracelets and chains, anklets, finger rings,
 - wrist-watch cases, watch straps and tighten-ers,
 - rivet buttons, tighteners, rivets, zippers and metal marks, when these are used in garments, if the rate of nickel release from the parts of these articles coming into direct and prolonged contact with the skin is greater than $0.5 \mu\text{g}/\text{cm}^2/\text{week}$; and
 - c. in articles such as those listed in point (b) where these have a non-nickel coating unless such coating is sufficient to ensure that the rate of nickel release from those parts of such articles coming into direct and prolonged contact with the skin will not exceed $0.5 \mu\text{g}/\text{cm}^2/\text{week}$ for a period of at least two years of normal use of the article.
2. Articles which are the subject of paragraph 1 shall not be placed on the market unless they conform to the requirements set out in those points."

It should be noted that the 0.5 micrograms nickel/cm²/week is as determined in the nickel release standard EN 1811 and it is understood that the release rates would not protect 100% of sensitized people from elicitation of ACD. However, clinical data indicates that the vast majority of sensitized individuals would not experience nickel ACD at this level of nickel release and individuals who were not previously sensitized would require substantially higher concentrations than 0.5 micrograms nickel/cm²/week to be released to the skin for nickel sensitization to occur.⁽¹⁷⁾

EN 1811:1998⁽¹⁸⁾ ("Reference Test Method for Release of Nickel from Products Intended to Come into Direct and Prolonged Contact with the Skin") originally came into force in 1998 and its use to test articles for nickel release was successful in removing from the market many unsuitable articles that could have caused nickel dermatitis. However, the test was not sufficiently reliable and reproducible. With CEN (Comité Européen de Normalisation, European Committee for Standardization) Mandate M414, a standardization working group (CEN TC 347 WG 1) was set up in 2007 with the objective of improving the test procedure. A modified procedure incorporating a corrigendum in May 2012 (EN 1811:2011)⁽¹⁹⁾ was approved, followed by an amendment in 2015 with the publication of the current EN 1811:2011+A1:2015. This amendment simplified the decision categories and provided a pass level of effectively 0.88 and $0.35 \mu\text{g Ni}/\text{cm}^2/\text{week}$ for articles and piercings, respectively, to account for the combined measurement of uncertainty.



Pink positive DMG test for nickel release from jeans' button.

In parallel, following a mandate by the European Commission (M448), CEN TC 170 WG8 has developed a new standard on nickel release testing from spectacle frames and sunglasses, EN 16128:2015 ("Ophthalmic optics. Reference method for the testing of spectacle frames and sunglasses for nickel release").

Also in used, though not approved for compliance testing, is the CR 12471:2002 standard, a "formalized" version of the DMG (dimethylglyoxime) test. It is a screening method to test for nickel release from alloys and coatings in items that come into direct and prolonged contact with the skin (a relatively easy, quick, and cheap method compared with EN 1811).

For coated products there is a requirement that the article should not release nickel above the specified limits after two years of normal use and this was covered by EN 12472:1998 (Method for the Simulation of Wear and Corrosion for the Detection of Nickel Release from Coated Item). This period of use was simulated by tumbling the articles in a mixture of abrasive paste and ceramic particles. However, this was judged too aggressive and, therefore, after considerable investigation, wood and nutshells replaced the ceramic particles and the method of tumbling was specified in more detail. This resulted in the re-issue of the standard as EN 12472:2005 and, after a corrigendum in 2009, as EN 12472:2005+A1:2009.

A very small part of the population is hypersensitive to nickel. These individuals react to lower concentrations of nickel on the skin than most nickel-sensitive individuals and potentially by oral exposure. Prevention of elicitation in these individuals is important and is done on a case-by-case basis. Regulation and prevention of nickel sensitization and nickel ACD of the general population is not intended to protect hypersensitive individuals.

6 WHAT IS THE NICKEL INDUSTRY'S POSITION CONCERNING NICKEL ACD?

The nickel industry:

- Recognizes that nickel ACD can be a significant health and social problem for individuals who have become nickel sensitized.
- Accepts the opinion of experts in dermatology that induction of nickel sensitization and nickel ACD is caused principally by body piercing or prolonged and intimate contact by the skin with a sweat-soluble form of nickel.
- Accepts and concurs with the opinion of experts that the use of nickel in ear-piercing studs, jewelry and clothing clasps, and zippers is the prevailing cause of nickel sensitization and nickel ACD. The nickel industry supports the intent of regulations such as the EU Nickel Directive (now REACH) to restrict the release of nickel from articles used in direct and prolonged contact with the skin and piercing studs.
- Supports the use of protective equipment and training for workers routinely handling nickel substances in industrial environments.
- Concurs with the Consensus Document from the 1997 Nickel Dermatitis Workshop that 'transient, short-term contact with nickel-containing articles such as coinage, keys, handles, tools, and other equipment does not appear to be a factor in the induction of an allergic contact dermatitis within the general population. If the contact is of short duration and infrequent, the risk of sensitization is negligible, and the risk of the elicitation of dermatitis is limited.'⁽⁴⁾
- Believes that adoption of regulations such as the Nickel Directive in the EU and Scandinavian countries have resulted in a reduction in the prevalence of nickel ACD.



Nickel is used in many coins around the world.*

- Is not aware of large numbers of cases of nickel ACD having been associated with nickel in coinage despite more than a century of use in billions of coins handled by billions of people. In particular, there is no epidemiological report of adverse effects in the Canadian population from having pure nickel 5, 10, and 25 cent coins in circulation for decades. In addition, there is no evidence of significant adverse dermatological effects in the United States population from having a 25% nickel-copper clad 25-cent coin.
- Believes that provocation studies where coins or tools are kept in intensive and prolonged contact with the skin of sensitized individuals and which elicit an allergic response are not relevant to coinage or tool use by the general population.

- Conducted a key study that demonstrated that continuous handling of nickel-containing coins for 8 hours/day for multiple consecutive days did not elicit a nickel ACD reaction in any of the nickel-sensitized or non-nickel-sensitized individuals tested.⁽²⁰⁾
- Understands that for the great majority of the general population, the use of tools is unlikely to result in a dose sufficient to cause nickel ACD or induce nickel sensitization.

7 PRESENT STATE OF SCIENTIFIC KNOWLEDGE

Nickel sensitization is not a new concern and has been studied by many groups. While there are still many questions on this issue to be answered, below is a summary of the current information.

- It is difficult to use animals to study nickel sensitization because animals display different immune responses than do humans. For ethical reasons, it is difficult to expose human subjects to a substance that may compromise their health. Scientists therefore have a dilemma. They would like to understand the mechanisms involved in human nickel sensitization, but they are not confident that the animals available for experimentation are good surrogates.
- The current thinking is that nickel by itself is not antigenic, but rather that nickel complexes involving histidines or proteins are bound to Langerhans' cells. These cells, located in the basal layer of the epidermis, actively participate in cutaneous immune regulation and surveillance and are responsible for antigen processing and presenting the antigen to T-lymphocyte cells. The bound Langerhans' cells migrate to regional lymph nodes where further processing of the antigen occurs and ultimately a population of altered nickel-specific T-lymphocytes are created and recirculated where they may enter peripheral tissue (including the skin). At this point the individual is "sensitized."
- In the sensitized individual, when antigen-specific T-lymphocytes encounter the antigen (*i.e.*, nickel ions), they release lymphokines, which are proteins that cause a wide variety of actions on other cells including stimulation of macrophages and natural killer cells and other responses. With a sufficient amount of stimulation, tissue inflammation and other allergic responses occur in an attempt to rid the body of the foreign entity. This integrated response is what causes the allergic contact dermatitis reaction.
- The condition of the skin is very important in nickel sensitization and nickel ACD. Intact skin with normal barriers is less susceptible (*i.e.*, less permeable to nickel ions) to developing nickel sensitization and nickel ACD than skin that is broken or otherwise abnormal regarding permeability of the skin. Heat, humidity, and increased sweat promote the likelihood and speed with which nickel ions are presented to the skin.⁽²¹⁾
- There is no known means of reversing immuno-activation (the sensitized condition). However, because the precise mechanism by which nickel ions and Langerhans' cells and T-lymphocytes interact is not understood, dermatologists are reluctant to conclude that such a reversal is biologically impossible. Knowledge about the mechanism may result in awareness of how to "turn off" the immune system to nickel.
- There is evidence that immunotolerance is possible. First, it is noteworthy that the nickel-producing and nickel-using industries very rarely have workers presenting symptoms of nickel ACD. It would be expected that a group of workers routinely coming into direct skin contact with various forms of nickel

metal and salts would display nickel ACD. The fact that it is not seen may be due to a tolerance that the workers acquire over time via an alternate route of exposure (inhalation or ingestion) that causes no allergic reaction by the immune system, even when higher nickel exposures are received later. Second, literature⁽²²⁾ indicates that dental braces made from high-nickel alloys (e.g., nickel-chromium with 60-80% nickel) resulted in nickel-tolerance in girls subsequently having their ears pierced compared to a higher prevalence of nickel sensitization in girls who had their ears pierced, but did not wear such dental braces prior to ear-piercing. This tolerance may be caused by a mechanism involving low nickel exposure orally over time. Third, immunotolerance in animals (mice) has been shown by nickel exposure either intravenously or orally, with T-lymphocytes in nickel-tolerant mice being transferable to other mice to make them nickel-tolerant.



Orthodontic braces may result in immunotolerance to nickel ACD.†

- Diagnosis of nickel-sensitivity is done via the patch test, which establishes contact of soluble nickel against a small portion of occluded skin. This is done under a specified procedure⁽²³⁾ to limit misinterpretation due to irritation rather than allergic response. An appropriate concentration of a solution of nickel sulfate is placed on a metallic or filter paper disc backed by aluminum foil (impermeable to water) and attached to the subject's upper back or upper arms by adhesive tape so that the skin area under test is completely covered. The patch is left in place for two days and then removed; the skin is evaluated for the severity of inflammation. Patch testing is capable of giving both false negative and false positive results. Nevertheless, it is by far the most routine diagnostic test for determining whether a person is nickel-sensitive along with history of reaction to nickel-releasing materials.
- In the 1960s another test, called the lymphocyte proliferation test (LPT), or the lymphocyte transformation test (LTT), was developed. Its advantage is that it uses a blood sample from a suspected nickel-sensitized individual and is performed *in vitro*, thus avoiding the risk of having nickel in contact with the skin and potentially sensitizing a non-nickel-sensitized person. The LPT (or LTT) is based on the fact that nickel-sensitized individuals have T-lymphocytes primed and ready for the nickel antigen being presented. The test pretreats the blood sample to concentrate the T-lymphocytes and then incubates them with a concentration of Ni. In the nickel-sensitive person, the presence of nickel will cause the primed T-lymphocytes to "turn-on" and elicit an immune response. They "turn-on" by doing several things, one of which is to divide rapidly (proliferate). If a radioactively labeled DNA precursor iododeoxyuridine is also present in the culture, the new T-lymphocytes will use this to synthesize new DNA for their daughter cells. Following separation of the T-lymphocytes, an increase in radioactivity above a measured control

(to account for normal cell division) is indicative of high cell proliferation, which means the original T-lymphocytes reacted to the nickel present. This test is only now becoming a clinical tool but more work is required to correlate it with patch test results and to make it reliable.

8 CONCLUSIONS

Nickel sensitization is a human health concern due to its marked prevalence in the general population. However, the risk of becoming nickel-sensitized or having a nickel ACD reaction (if already nickel-sensitized) can be managed and minimized through reduced exposure to nickel-releasing items. In the workplace, exposure reduction includes personal protective equipment and other risk management measures. For consumers, exposure can be reduced through restriction of direct and prolonged exposure to items releasing nickel in amounts greater than the threshold for nickel ACD.

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9.1 ADDITIONAL REFERENCES

Additional information on nickel allergy is available from the Nickel Institute

<https://www.nickelinsti-tute.org/~link.aspx?id=73D3191D8BFE460797012B60D536363A&z=z> (last accessed June 2016)

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Fact Sheets on Nickel and Human Health

This is the first in a series of fact sheets addressing issues specific to the evaluation of risks to humans associated with nickel-containing substances and materials. The fact sheets are intended to assist the reader in understanding the complex issues and concepts associated with assessment of human health hazards, dose-response relationships, and exposure by summarizing key technical information and providing guidance for implementation.

NiPERA welcomes questions about the concepts and approaches implemented for nickel allergic contact Dermatitis. For inquiries, please contact:

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