Prevention of Nickel Allergy by Regulation of Specific Exposures*†

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ABSTRACT

Nickel allergy is a cell-mediated immune response. Most cases of nickel allergy can be related to skin contact with nickel containing metallic items as buttons, suspenders, ear-ornaments etc. Epidemiological studies have shown a sensitization frequency of 20 percent in young females and 10 percent in the elderly. Two to four percent of males are sensitized.

The biological significant parameter is not the nickel concentration in the alloy or coating but the amount released to the skin during exposure to human sweat. A threshold of 0.5 μg/cm²/week has been established, where only a minor part of the nickel sensitive will react.

A legislation limiting nickel exposure from specific consumer items is in force in Denmark. An expanded exposure regulation was adopted, but not yet implemented, by the EU-countries in 1994.

Introduction

Contact allergy (sensitization) is a cell-mediated immune response. Contact sensitization includes two steps—induction and elicitation. When a chemical (e.g., nickel) penetrates the skin, it will be absorbed by a specialized dendritic cells in the epidermis—the Langerhans cell—which then moves to the regional lymph nodes. Here the chemical will be presented to naive T-lymphocytes, and a sensitization specific to the chemical in question will take place. The next time the individual is exposed to this chemical, the Langerhans cells will present the chemical to the specific sensitized T-lymphocytes in the epidermis and elicit the inflammatory response. The outcome of this process is the skin disease acute allergic contact dermatitis illustrating redness, oedema and vesiculation.

Contact Allergy

Contact sensitizing chemicals are substances with a molecular weight generally below 300 to 400. It is not possible to identify sensitizing chemicals from the

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chemical structure, but sensitization studies are needed either in animals or humans. Most important as to whether or not sensitization occurs is the inherent sensitizing capability of the chemical, the concentration per cm², and the individual propensity to develop contact sensitization.³,⁴

Contact allergy can be diagnosed either by an in vitro test or by an in vivo test. The most commonly employed in vitro test is the lymphocytic transformation test. The principle is that sensitized T-lymphocytes incorporate radioactive thymidine at a greater rate compared to non-sensitized.⁵ In vitro testing is not developed for routine use. The patch test is used for clinical routine. The individual is exposed on the back to a small amount of the chemical in question under occlusion for 2 days. The appearance of a 2 cm² large eczematous spot in the test area confirms contact allergy.⁶

Contact allergy is common in the general population and not unexpectedly even more common in patients with eczematous skin disease. In North America, contact allergy to the plant poison ivy affects 50 to 70 percent of the population.⁷

Patch testing in a non-selected part of the Danish population showed that 15.2 percent are sensitized to one or more environmental chemicals.⁸ The most frequent item is nickel, followed by fragrances, preservatives, rubber chemicals, and medicaments. Nickel is the most frequently diagnosed contact allergen when patch testing patients with skin diseases.

Nickel Exposure

In nature, nickel is bound in sulphitic and oxidic ores, often together with cobalt, copper, platinum, and gold. Nickel in nature does not exist in ionic form and, therefore, does not act as a huten (allergen). Nickel has been found in prehistoric Chinese weapons.¹⁰ After nickel was first isolated by Axel Cronstedt in 1756, a wider industrial use took place, in the beginning as nickel plating and from the end of the 18th century as stainless steel. The development of the automotive industry at the start of this century increased the demand for nickel alloys, particular stainless steel.¹⁰ Since the 1920s, nickel plating has been used for articles which are in prolonged contact with the skin, i.e., buttons, suspender, wrist watches, and inexpensive jewelry.

The dimethylglyoxime test is widely used by dermatologists to identify metallic items that might elicit nickel dermatitis in nickel allergic subjects.¹¹,¹² The basis for the test is the pink colour of the dimethylglyoxime-nickel complex in a basic environment. This test is easy and inexpensive to carry out but gives some doubtful and false negative results. The sensitivity of the test can be improved by pretreating the metallic item with synthetic sweat and heating it to 50°C.¹³

The reference method to evaluate significant nickel for contact dermatitis is the amount of nickel released from a metal surface by human sweat measured by atomic absorption.¹⁴ The risk of a nickel alloy eliciting allergic reactions in nickel sensitized individuals correlates with the amount of nickel released.¹⁵

Methods to evaluate individual nickel exposure need to be developed. It has been shown that the nickel content in nails varies significantly, depending on the degree of occupational nickel exposure.¹⁶ Interestingly, nickel nail measurements can identify a repeated nickel exposure from 1 ppm nickel solution. This concentration does not elicit hand eczema in nickel allergic individuals.¹⁷ Similarly, nickel accumulates in the keratin at the stratum corneum in the skin. Preliminary studies indicate that skin exposure to nickel can be quantified by
an analyzing the nickel concentration in stratum corneum obtained by repeated tape stripping.\textsuperscript{19}

**Contact Allergy to Nickel**

Contact allergy to nickel is not inborn but is a result of skin exposure to soluble nickel salts.\textsuperscript{19} A systemic exposure to nickel orally or by inhalation in non-contact allergic individuals leads to specific immunologic tolerance, meaning that the individual is unable to develop contact allergy to the metal at a later stage.\textsuperscript{2} Systemic nickel exposure in contact allergic individuals might result in systemic contact dermatitis reactions (generalised eczema) in a dose dependent manner.\textsuperscript{16}

Nickel dermatitis was first described among German workers exposed to nickel baths containing nickel sulphate and nickel chloride. Nickel allergy has been common since the 1930s, primarily in females sensitized by nickel released from inexpensive nickel plated jewelry. Today 20 percent of young females are nickel-sensitized and as are 10 percent of the elderly female generation. Approximately 2 to 4 percent of males are also nickel sensitized.\textsuperscript{8} The frequency varies at different parts of the world depending on the use of nickel-plated consumer articles. Primary occupational nickel sensitization is rare today. Individuals primarily nickel-sensitized from consumer items may later develop hand eczema when occupationally exposed to the metal.\textsuperscript{20}

Clinically, nickel dermatitis appears at metal contact sites such as earlobes, arm wrists, abdomen, and the hands. In heavily exposed individuals, nickel dermatitis might spread to secondary regions.

**Dose Response in Nickel Allergy**

The quantitative aspects of nickel dermatitis have recently been reviewed.\textsuperscript{21} Clinically and scientifically, nickel allergy is defined as a positive patch test to 5 percent nickel sulphate in petrolatum.\textsuperscript{22,23} This test concentration will diagnose most cases of nickel dermatitis and the obvious cases of occupational nickel hand eczema. Using higher test concentrations either epicutaneously or intracutaneously has shown that individuals without clinical symptoms may react to nickel.\textsuperscript{23,24} The lymphocytic transformation test is raised in a number of control persons (negative nickel patch test) particularly among those with a history of earlier metal contact dermatitis.\textsuperscript{5} These studies indicate that subclinical nickel sensitization exists. The clinical significance of this phenomenon in relation to induction and elicitation of nickel allergy is unexplored.

Experimental induction of contact allergy to nickel in humans is difficult. Repeated exposures to high nickel concentrations (10 to 15 percent) combined with irritants are needed. Using different methodologies, a sensitization rate of 10 to 50 percent has been reached.\textsuperscript{24,25} Nickel concentrations able to elicit an allergic response in already sensitized individuals is lower. Approximately 10 percent of those sensitized react to concentrations below 0.04 percent nickel.\textsuperscript{26}

A few studies have examined in vitro nickel release in artificial sweat from items either inducing or eliciting nickel allergy. The nickel release has been uniformly high.\textsuperscript{21} A number of studies have performed nickel release and skin exposure with commonly used nickel alloys and nickel coatings including both controls and nickel sensitized individuals. There is a linear correlation between the amount of nickel release expressed as $\mu g/cm^2/week$ and the percentage of nickel sensitized individuals giving a positive skin reaction. However, for some alloys the correlation between the in vitro nickel release and the reactivity in sensitized individuals are unpredictable.
TABLE I
Summary of the Nickel Directive* and the Proposed Analytical Methods

<table>
<thead>
<tr>
<th>Nickel May Not Be Used</th>
<th>Proposed Analytical Method</th>
</tr>
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<tbody>
<tr>
<td><strong>Part 1</strong></td>
<td>Atomic absorption spectroscopy.</td>
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<tr>
<td>In posts for ear-piercing used during epithelization, unless they are homogenous and the concentration of nickel is less than 0.05%.</td>
<td>Atomic absorption spectroscopy.</td>
</tr>
<tr>
<td><strong>Part 2</strong></td>
<td>Reference test method for release of nickel.</td>
</tr>
<tr>
<td>In products intended to come into direct and prolonged contact with the skin, such as earrings, necklaces, wristwatch cases, watch straps, buttons, tighteners, zippers, etc., if nickel release is greater than 0.5</td>
<td>Analysis of nickel released in artificial sweat. Screening test for nickel release.</td>
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<tr>
<td>laces, wrist watches, and buttons. A similar history was obtained in 12 of 100 consecutive patients with a negative patch test to nickel. Some of these cases will represent an irritant response, and in some cases there is weak nickel sensitization not identified by the routine patch testing with 5 percent NiSO₄*. This study confirms clinical studies carried out by dermatologists since the 1930s. Based on the knowledge that primary nickel sensitization is caused by a limited number of products and the fact that a nickel threshold concentration of 0.5 μg/cm²/week has been defined by reactions of only few nickel sensitized individuals, legislation has been implemented in Denmark to regulate the exposure to nickel. As the concentration</td>
<td></td>
</tr>
<tr>
<td><strong>Part 3</strong></td>
<td>Wear and corrosion test for the detection of nickel release from coated items. A modified test used in the watch industry, and the screening test for nickel release.</td>
</tr>
<tr>
<td>In coated products, as in part 2, unless the coating is sufficient to ensure that the nickel will not exceed 0.5 μg/cm²/week after two years of normal use.</td>
<td>Wear and corrosion test for the detection of nickel release from coated items. A modified test used in the watch industry, and the screening test for nickel release.</td>
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* (94/27/EC, 12th Amendment of Directive 76/769/EEC)

Generally, high class stainless steel elicits no or few reactions in nickel sensitized individuals. The studies confirm that nickel alloys or coatings releasing less than 0.5 μg/cm²/week in synthetic sweat are safe for most nickel sensitized individuals.¹⁵,²⁷,²⁸,²⁹,³⁰

Prevention of Nickel Allergy

Nickel dermatitis has been identified as a significant problem for decades because of the high frequency and the risk of associated long standing hand eczema.²⁰,²²,³¹,³² In most cases of sensitization, the patients can recall an episode of contact dermatitis derived from a metallic item. In a recent study of 112 consecutive nickel sensitive patients, only 5 did not give a history of former or present contact dermatitis from contact with metallic items designed to be in prolonged skin contact, i.e., earrings, necklaces, wrist watches, and buttons. A similar history was obtained in 12 of 100 consecutive patients with a negative patch test to nickel. Some of these cases will represent an irritant response, and in some cases there is weak nickel sensitization not identified by the routine patch testing with 5 percent NiSO₄*. This study confirms clinical studies carried out by dermatologists since the 1930s.²²

Based on the knowledge that primary nickel sensitization is caused by a limited number of products and the fact that a nickel threshold concentration of 0.5 μg/cm²/week has been defined by reactions of only few nickel sensitized individuals, legislation has been implemented in Denmark to regulate the exposure to nickel. As the concentration

* Menné T. Reactions to metallic consumer items in nickel patch test positive and negative eczema patients (unpublished).
of primary nickel sensitization is higher than the concentration of elicitation, the regulation is expected to prevent most cases of primary nickel sensitization.

In 1994 an European Union-legislation was adopted having the same intention and based upon the same ideas but having a higher degree of consumer protection by giving a stricter regulation of ear-piercing equipment. This procedure is particularly risky with respect to nickel allergy. A paragraph on the durability of coatings is also included in the legislation.

The summary of the European Union-legislation and the suggested control methods are given in table I. This legislation is expected to come into force within 1 to 2 years, depending on agreement of control methods, which include the dimethylglyoxime test (and modifications), nickel release in artificial sweat quantified by atomic absorption, and provocation test simulating 2 years of normal use.

References


