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Nickel skin levels in different occupations and an estimate of the threshold for reacting to a single open application of nickel in nickel-allergic subjects

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Summary

Background: Nickel is a frequent allergen throughout the world. However, it has been unclear the extent to which nickel is relevant as an occupational contact allergen as opposed to simply being a reflection of jewellery exposure. Some thresholds for cutaneous nickel exposure to induce a dermatitis reaction in nickel-allergic individuals have been defined. Over recent years it has become possible to accurately measure the quantity of nickel on the skin of individuals in a number of occupations.

Objectives: In this study we aimed to measure the quantities of nickel on the skin of the fingers in workers employed in occupations for which nickel has been suspected as a contact allergen. In addition, we aimed to define the threshold for a dermatitis reaction for the single application of a quantity of nickel to the skin of nickel-allergic individuals when read at 2 days.

Methods: We employed the 'finger immersion' technique for sample collection and induction coupled plasma mass spectrometry for the nickel measurement. Nickel platers, cashiers, sales assistants, caterers, health care assistants, office workers, dental nurses and hairdressers were studied (5 in each group except for 7 cashiers). A correction was made for the fact that the finger immersion method underestimates the amount of nickel on the fingertip. The threshold for reactivity to a single application of nickel was studied by the application of various concentrations of nickel (0.05 mcg/cm² (2 subjects), 0.05 mcg/cm² (2 subjects), 2.5 mcg/cm² (3 subjects), 5.0 mcg/cm² (21 subjects), 15 mcg/cm² (19 subjects), 30 mcg/cm² (19 subjects) and 45 mcg/cm² (18 subjects) in 21 subjects overall using Finn chambers on forearm skin. The reading was made at 2 days and reactions were graded using the ICDRG classification.

Results: Nickel levels on fingers in platers, cashiers, sales assistants, caterers and even office staff, are at or above the 0.035mcg/cm² level at which 22% of nickel allergic subjects will react (after applying a correction). The single open application of nickel study demonstrated a dose-response relationship, with no subjects reacting to 2.5 mcg/cm² or less, but increasing numbers reacting at the higher concentrations as follows: 6 of 21 (28%) at 5.0 mcg/cm², 6 of 19 (31%) at 15 mcg/cm², 7 of 19 (37%) at 30 mcg/cm² and 11 of 18 (61%) at 45 mcg/cm².

Conclusions: This study confirms that nickel levels on the skin in coin handling occupations and some others are sufficient to induce an allergic contact dermatitis in some nickel-allergic subjects. A single application of 5 mcg/cm² when read at 2 days induced a dermatitis reaction in 6 of 21 nickel-allergic subjects.

Introduction

Nickel is a common allergen on patch testing in western countries affecting 10% of women and 1-2% men.¹ Women are thought to be sensitized through ear piercing and the wearing of nickel-releasing costume jewellery.² Nickel allergy is important because of its relationship with vesicular hand dermatitis, noted for more than 50 years, although the association is complex.^{3,4}

The European Union has attempted to regulate nickel levels in consumer products. The EU Directive on Nickel (76/769) states that post assemblies for newly pierced ears should have a nickel content of <0.05%, metal products in direct prolonged skin contact should have nickel release of <0.5 mcg/cm²/week and non-nickel coating of these products should last at least 2 years.^{5,6} This Directive was updated by an annex in which the nickel release of all post assemblies which are inserted into pierced ears and other pierced parts of the human body was required to be less than 0.2 mcg/cm²/week.

This legislation may have had some effects on consumer exposure and rates of nickel allergy in the general population. Nickel continues to have potential as an occupational allergen and a cause of industrial hand dermatitis in some industries.² Nickel sensitivity in nickel-platers was once common but is now rare due to improvements in workplace practices.⁸ In workers such as cleaners, caterers, bar staff and hairdressers, who may be exposed to lower levels of nickel, the role of nickel as a contact allergen has been difficult to evaluate.⁹⁻¹³

Discussion of nickel exposure both in the consumer and industrially lead to a consideration of the threshold levels of nickel on the skin at which nickel-sensitive subjects will develop a dermatitis reaction. These can be difficult to determine and depend on several factors, e.g. whether the skin is occluded (as in a patch test) or irritated (i.e. inflamed).¹⁴ When comparing skin exposure elicitation thresholds for water-soluble nickel, the solubility of the nickel compounds must be considered as only nickel ions can cause a dermatitis reaction. 'Water insoluble' nickel substances do release some nickel ions into sweat, and therefore are not completely 'insoluble'. It is often difficult to compare studies due to variations in methodologies.

Occupational hygiene evaluation of work surface contamination has traditionally employed either the wipe sampling or the tape stripping methods in conjunction with atomic spectrometric techniques.^{15,16} Wipe sampling is generally less effective at removing skin contaminants than analogous washing methods which usually involve immersing the hand in a bag or bowl of solvent with extract transfer to a sample tube for analysis.¹⁷ However, the recovery by the acid wipe sampling technique of metals applied to the skin is more than 90%.¹⁸ Previously we have described a sampling method for finger skin using immersion of fingers in a test tube of purified water with analysis by induction coupled plasma mass spectrometry.¹⁹ This method showed skin nickel levels shown to be <10 mcg/L in 'normal' subjects, whereas in certain

occupations the levels ranged from <10-1310 (ng/cm²) in nickel refiners <10-1310, 20-7159 in nickel platers, <10-65 in cashiers and <10 in hairdressers and bar staff.

Coin handling has been considered as a risk factor for the development of nickel hand dermatitis. A study using bi-coloured 2 Euro coins (made of Cu 75%, Zn 20%, Ni 5%: nickel released in artificial sweat 86 mcg/cm² over 1 week) showed that, after coin handling for 1 hour, sampling by acid wipe of fingers (and analysis by inductively coupled plasma mass spectrometry) revealed levels of nickel at 0.09-4.1 mcg/cm² on skin especially on the volar aspect of the fingertips.²⁰ These authors believe this indicates sufficient nickel may be on the fingers from coin handling to produce a dermatitis.

In this study we considered the problems of the threshold at which nickel allergic subjects react and the difficulties in measuring the amounts of nickel on the skin. We aimed to re-evaluate the levels of nickel on the skin of the hands in various occupations with special reference to expressing the result per unit area of exposed skin. In addition, we proposed to establish the threshold in nickel-allergic subjects for a dermatitis reaction to a single open application of nickel to better understand at what level a nickel-allergic person might react when exposed to a single challenge of nickel to their skin.

Materials and methods

Sampling of concentration of nickel on the skin of the dominant side index finger and thumb in various occupations

The collection technique of 'finger in test tube of water' which allows rapid sampling to measure the amount of nickel on the skin has already been described.¹⁹ Details of the technique used are as follows. The subjects' thumbs and forefingers were carefully immersed into two separate 50ml plastic tubes containing 35ml high purity water for two minutes with gentle agitation. The tubes were of a size that permitted all sizes of thumbs and fingers to enter. After sampling, nitric acid (35ml) was added to each sample to stabilize extracted nickel and all samples were stored at 4°C prior to analysis. The surface areas (in cm²) of the finger or thumb were calculated by measuring the dimensions of the digit (i.e. the length (l) immersed and the radius (r) derived from the width), using a modification of the formula for calculating the surface area of a cylinder (counting one end only), i.e. πr^2 plus $2 \pi r l$. Samples were collected without hand washing after workers had carried out their normal daily tasks for at least one hour. If subjects had washed their hands, e.g. they had visited the toilet, they were not sampled until at least an hour had passed after their episode of hand washing. The occupations studied were nickel platers, cashiers, sales assistants, caterers, office workers, dental nurses, healthcare assistants, and hairdressers (5 in each group except 7 cashiers). All subjects gave written consent.

Spectrometric analysis

The analysis of the amount of nickel was done by induction coupled plasma mass spectrometry after extracts were stabilised using nitric acid.. An axially viewed SpectroCiros^{CCD} inductively coupled plasma-optical emission spectrometry (ICP-OES) spectrometer (Spectro Analytical, UK) utilizing the Ni 231.604 nm line was used for analysis. Background corrections were applied. The instrumental limit of detection (LOD) for Ni, calculated as 3 standard deviations of 10 blank (1% Aristar nitric acid in Millipore water) measurements, was 1.3 mcg/l. The lower level of quantification (LLOQ) was 4.2 mcg/l. Both a quality control standard (50 mcg/l Ni, mean = 49.8 mcg/l, RSD = 1.0%, n = 12) and a certified reference solution, NIES-1643d (58.1 mcg/l Ni, mean = 53.3 mcg/l, RSD = 1.1%, n = 5), determined periodically between samples, gave good precision and accuracy over a 5 hour analysis run confirming the robustness of the ICP measurement method employed. The method allowed quantification of the amount of nickel per unit surface area in mcg/cm² (Table 1). The sampling efficiency of this method was not studied.

Corrective factor

One problem with this method of sampling (highlighted by Liden et al) was that it averages the amount of nickel over the whole finger, whereas most nickel will be concentrated on the volar aspect of the terminal phalanx which was found in a sample of 12 individuals to make up 8% and 12% respectively of the surface areas of the index finger and thumb respectively.²⁰ Hence a correction was applied that made the assumption that all nickel was located on palmar terminal phalanx.

Determination of the threshold for reactivity for the single application of quantities of nickel to forearm skin in nickel-allergic subjects.

In the second part of the study, the threshold for a clinical reaction of dermatitis was assessed in 21 patients attending for patch testing as part of their routine investigation, who were shown to be allergic to nickel (with at least a + allergic reaction according to the ICDRG classification).²¹ A dose-response study was performed on normal-looking forearm skin applying four increasing concentrations of nickel to surface areas of 0.8cm² using a plastic-covered paper card template (applied to the volar aspects of the non-dominant arm, 10cm up from the wrist) and reading the results at 48 hours. The nickel solutions were applied using a micropipette as a 5 microlitre droplets onto the circles of skin exposed by the template. The meniscus of the droplet was broken up using the side of the pipette. The droplets were allowed to dry by evaporation. The template was then removed. The sites on the forearm were marked, then photographed and coded.

The reactions were graded according to the ICDRG classification (and photographed).

²¹ The concentrations of nickel ion tested (using aqueous solutions of nickel sulphate) with the number of subjects tested (in parenthesis) were 0.05 mcg/cm² (2 subjects), 0.5 mcg/cm² (2 subjects), 2.5 mcg/cm² (3 subjects), 5.0 mcg/cm² (21 subjects), 15

mcg/cm² (19 subjects), 30 mcg/cm² (19 subjects) and 45 mcg/cm² (18 subjects). Two subjects were tested with the lowest concentrations first as a range-finding exercise. When it was apparent that they did not react, we focussed on the higher range of concentrations in order to maximize our results.

Governance

Both parts of the study were approved by the Sheffield Ethics Committee (Ethics no. 06/Q2305138) and the Research Office of Sheffield Teaching Hospitals NHS Foundation Trust, who also audited the study (STH no. 14578).

Results

Levels of nickel on the skin of fingers and thumbs in different occupations

The study showed that appreciable amounts of nickel were present on the fingers of nickel platers (unsurprisingly), cashier, and sales assistants, and caterers (Table 1). Without a correction, nickel levels on fingers in platers are above the 0.035mcg/cm² level at which 22% of nickel allergic subjects will react (according to Fischer et al) with cashiers and sales assistants at a half of this. However, these levels will underestimate the quantities of nickel on the fingertips.²²

Applying the correction showed that nickel levels on fingers in platers, cashiers, sales assistants, caterers and even office staff, are at or above the 0.035mcg/cm² level at which 22% of nickel allergic subjects will react.

Threshold for reactivity to a single open application of nickel

The study demonstrated a dose-response relationship, with no subjects reacting to 2.5 mcg/cm² or less, but increasing numbers reacting at the higher concentrations. The grade of reactivity increased with increasing concentration of nickel (Table 2; Fig 1). The percentages who showed a dermatitis reaction at the test site (of ?+ or more) were as follows: 6 of 21 (28%) at 5.0 mcg/cm², 6 of 19 (31%) at 15 mcg/cm², 7 of 19 (37%) at 30 mcg/cm² and 11 of 18 (61%) at 45 mcg/cm².

Considering reactions of + or more (by the ICDRG classification), 1 of 21 reacted at 5mcg/ cm², 3 of 19 at 15 mcg/cm², 5 of 19 at 30 mcg/cm², and 5 of 19 at 45 mcg/cm². The study demonstrated that there was quite a wide range of reactivity between individuals all of whom had been shown to be nickel-allergic on patch testing.

Discussion

Our study provides some evidence that skin nickel levels in some workers especially coin handlers, can approach those where dermatitis could be induced in some cases according to the available evidence for repeated exposure. However, we demonstrated

that the threshold for a single application of nickel is much higher, at least 5 mcg/cm² in most subjects.

Methodology

The finger immersion method is a simple technique for the measurement of nickel on a defined surface area of skin.²⁰ However, it has become apparent that it has an inherent weakness which is that it gives a mean value over the whole digit and the principal area of exposure, usually the palmar fingertip, is not specifically sampled. It has been shown that nickel levels on skin can vary by a factor of several-fold (Jansen 2008). Hence it would seem that the acid wipe sampling method appears to be the best technique for assessing nickel quantities on specific areas.^{20,23} We introduced a correction after considering the underestimate that our finger immersion method would produce as explained above. Using the correction the results we obtained were very similar to those of other researchers.

Hand dermatitis

There is some evidence that the risk for hand eczema in women who are nickel-allergic may previously have been overestimated. In an epidemiological study, the risk for hand eczema in women positive to nickel on patch testing with no history of childhood eczema was doubled, but no statistical difference was found between women who were patch test-positive and patch test-negative to nickel for occurrence of hand eczema.²⁴ The most important risk factor for hand eczema was a history of childhood eczema. Nonetheless many authors accept that nickel is an important contact allergen for principally hand dermatitis in several occupations.²⁵ Recent work has convincingly shown that the levels of nickel measure on the skin can exceed the thresholds required for induction of dermatitis in nickel-allergic subjects.²⁵ Lidén and colleagues have shown that the amounts of nickel deposited on the skin of carpenters, locksmiths and cashiers were sufficient to induce an allergic contact dermatitis. Repeated coin handling is associated with significant amounts of nickel accumulating on the skin of the fingers in contact with the coins.²³

Occupation

Cashiers and shop assistants in money-handling occupations are regularly exposed on their hands to nickel (albeit in small quantities) extracted by sweat from coins made from alloys containing appreciable amounts of the metal (5-25% Ni).²⁶ Nickel has been suggested as a potential cause of hand dermatitis in this occupational group. In a study, repeated daily exposure of the hands of nickel-sensitive patients to nickel (100 mg/L aqueous solution) can result in worsening inflammation.²⁷ Healthy volunteers were unaffected by the same levels, which were said to simulate trace to moderate occupational nickel exposure.

We have demonstrated appreciable amounts of nickel were present on the fingers of nickel platers (unsurprisingly), cashiers, sales assistants, and caterers. Interpretation of threshold levels need to be confirmed, but our study provides some evidence that skin nickel levels in some workers especially coin handlers, can approach those where dermatitis could be induced in some cases. Our actual figures obtained after the correction are very similar to those described by Lidén et al and Jensen et al.^{20, 23, 25}

Our study confirms that nickel-allergic workers who handle coins, i.e. cashiers and sales assistants, potentially accumulate sufficient nickel on their skin to develop an allergic contact dermatitis. Some office staff and caterers may also be at risk. The exact predisposition will depend on the type of work they do and the contact with nickel in their workplace. However, in hairdressers the levels of nickel on the skin appeared to be below the threshold. The situation for health care assistants and dental nurses were equivocal and require clarification.

EU legislation

Based on the proposed risk of subsequent hand dermatitis in nickel-allergic subjects, the European Union (EU) introduced legislation to control nickel in consumer products. There is some evidence that this legislation has had an effect as in Denmark a decrease in the association between nickel allergy and hand dermatitis has been reported among young women.²⁶ The decrease in prevalence of nickel allergy in Denmark started before the EU legislation came into effect, due it is supposed to the introduction of the limitation of nickel release to Denmark in 1990.²⁷ In the UK, data are difficult to obtain but the number of cases of occupational dermatitis reported to EPIDERM in which nickel was suggested as a possible factor has declined over the last 5 years (personal communication, R Agius: EPIDERM, University of Manchester; Fig 2), although a decline in manufacturing industries might also have contributed to this. EPIDERM is a British-based reporting system for the prevalence of occupational dermatitis, consisting of a core of 20 monthly reporters and a sample for one month of the year from the other 500 dermatologists in the UK. The results obtained are an estimate of the prevalences and not actual.

Threshold

The question of threshold for reactivity in nickel-allergic subjects is an important but complex matter. Naturally there will be inherent variations in threshold between individuals but there are also differences in the type and duration of exposure and in the biological properties of the skin that is exposed. Whether the skin is occluded or not, and exposed repeatedly or on a single occasion will also make a difference. Occluded, as in a patch test, the level at which 50% of patients allergic-positive on patch testing to 5% $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in pet. react was found to be about 0.5% (equivalent to 26.4 mcg/cm² ionic nickel) for water soluble nickel compounds.³⁰ The lower level at which about 10% of nickel-allergic subjects reacted was 0.01% (100 parts per million, equivalent to 530 ng/cm²) and the lowest detectable threshold was 5 parts per million (26 ng/cm²).³⁰

However, using 'TRUE test' which employs a different allergen delivery system, the median threshold was 3 mcg/cm² with the lowest threshold being 100 ng/cm².³¹ Unoccluded, as in an open application test, for water soluble nickel compounds the lowest threshold was found to be five times higher at 53000 parts per million (the authors do not give a figure in ng/cm²).³² In a repeated open application test applying a nickel solution twice daily, Fischer et al found that at 1 week the percentage of nickel-allergic subjects who reacted to nickel applied to their skin were 83% at a concentration of 3.5 mcg/cm², 56% at 0.35 mcg/cm², and 22% at 0.035 mcg/cm².²² For a single patch test using NiSO₄.6H₂O in 10% ethanol /90% water, Fischer and colleagues found that 10% of nickel-allergic individuals reacted to 0.78 mcg/cm² nickel.²²

There have been no previous studies of the threshold for reactivity for a single open application of nickel in nickel-allergic subjects. Not surprisingly, the quantity of nickel required to elicit a response in this situation was higher than that required for an occluded patch test or a repeated open application test. Considering a + reaction (by the ICDRG classification) only 1 of 21 tested subjects reacted at 5mcg/cm² although 5 had a ?+ reaction. Reactivity increased as anticipated with increasing quantities of nickel, so that 5 of 19 had a + or ++ reaction at 30mcg/cm² (Fig 2).

Conclusion

In conclusion, our study has confirmed that nickel levels on the skin in coin handling occupations and some others are sufficient to induce an allergic contact dermatitis on some nickel-allergic subjects. In addition, our single allocation threshold study demonstrates some reactivity to a single application of 5 mcg/cm² when read at 2 days. Further studies of occupational levels of nickel not only on the skin but also on workplace surfaces should be helpful in reducing industrial exposure.

Acknowledgement

This study was supported by a research grant from the British Skin Foundation and the British Contact Dermatitis Society.

What is known about this?

- Nickel levels on the skin in some occupations can exceed the quantities needed to induce an allergic contact dermatitis in nickel-allergic subjects.
- The threshold for a nickel-allergic individual reacting to nickel is variable but 22% will react to a nickel quantity of 0.035 mcg/cm².

What does this study add?

- This study confirms that nickel levels on the hands of nickel platers, cashiers and shop assistants are of an order sufficient to induce a dermatitis in a proportion of nickel-allergic individuals.
- This study demonstrates that the lowest threshold for a single application of nickel to induce any dermatitis reaction is 5 mcg/cm² when assessed at 2 days.

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Captions to Tables

Table 1. Nickel levels on the skin of the index finger and thumb of subjects in a variety of occupations as measured using the finger immersion method. The corrected levels have been corrected because the finger immersion method underestimates the amount of nickel on the distal palmar aspects of the digit since it assumes an even distribution of nickel over the entire surface area of the digit. The formula used for correcting this is explained in the text. The uncorrected and corrected nickel levels on skin of the thumb and index fingers are shown as mcg/cm^2 (combined means, with standard deviations, SD; n is number tested)

Table 2. Number of nickel-allergic subjects who developed a dermatitis reaction to a single open application of ionic nickel at various concentrations and the grades of reaction they showed according to ICDRG criteria (graded as: no reaction = 0, ?+ = 1, + = 2, ++ = 3, +++ = 4)

Captions to figures

Fig 1.

The graduated response after the single application of nickel when assessed at 2 days after application the quantitative of nickel applied are from the left: 5 mcg/cm^2 , 15 mcg/cm^2 , 30 mcg/cm^2 , and 45 mcg/cm^2 .

Fig 2.

Data showing the decline in the numbers of cases where nickel is considered as a possible contributor to occupational dermatitis as reported annually to EPIDERM (University of Manchester) 1999 to 2009 (personal communication, Professor R Agius).



Fig 2:

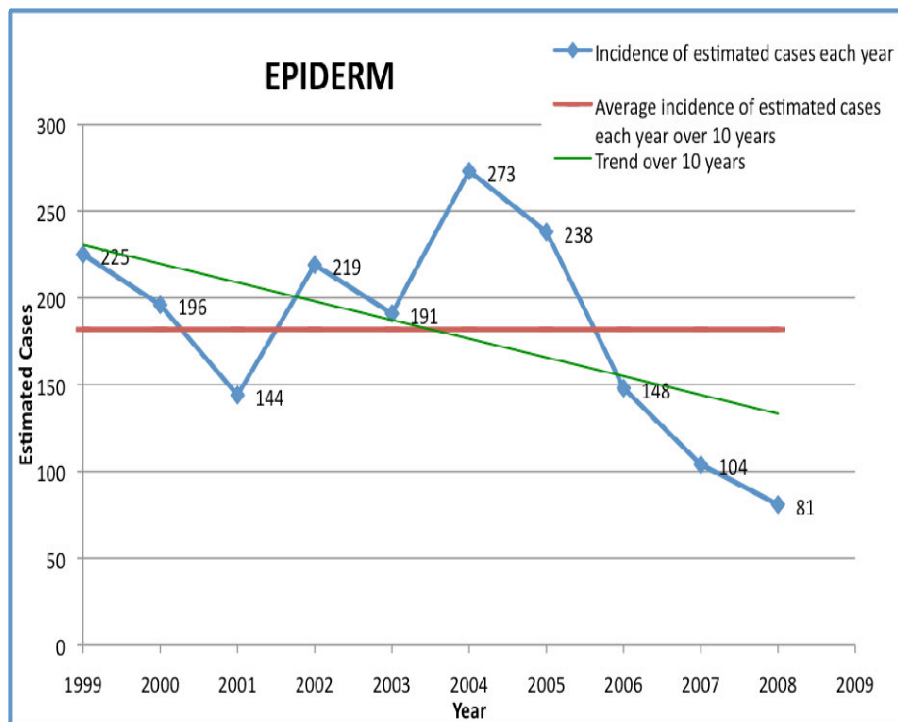


Table 1

	Uncorrected			Corrected		
	n=	mean	SD	n=	mean	SD
Electroplaters	5	0.240	0.150	5	1.820	1.230
Cashiers	7	0.017	0.011	7	0.146	0.092
Sales assistants	5	0.014	0.015	5	0.100	0.092
Caterers	5	0.008	0.007	5	0.062	0.057
Office staff	5	0.007	0.002	5	0.058	0.021
Dental nurses	5	0.005	0.002	5	0.037	0.017
Healthcare assistants	5	0.003	0.002	5	0.037	0.046
Hairdressers	5	0.003	0.001	5	0.023	0.009

Table 2

Nickel concentration (per cm ²)	Number tested	Grade of reaction				
		0 (-)	1 (?+)	2 (+)	3 (++)	4 (+++)
0.05 mcg	2	2	0	0	0	0
0.5 mcg	2	2	0	0	0	0
2.5 mcg	3	3	0	0	0	0
5.0 mcg	21	15	5	1	0	0
15 mcg	19	13	3	1	2	0
30 mcg	19	12	2	2	3	0
45 mcg	18	7	6	2	2	1