Acta derm.-venereol. 49: 14–19, 1969

THE RELATIVE IMPORTANCE OF VARIOUS ENVIRONMENTAL EXPOSURES TO NICKEL IN CAUSING CONTACT HYPERSENSITIVITY

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Nickel sensitization and detergents were recently discussed by Malten *et al.* in this journal (10) and the present paper should be considered in conjunction with that study. The present investigation deals with some clinical and epidemiological aspects of environmental exposures to nickel.

Nickel contact hypersensitivity ranges high among the increasing group of contact eczemas. At the out- and in-patient clinic of the Nijmegen University positive nickel patch tests are found in 4 % to 9 % of those suspected to be suffering from contact eczema (table 1). This observation is similar to experiences of clinics in other countries of the world (1, 4, 12, 18) though in Munich nickel hypersensitivity is reported to be rare (2). This may be related with hitherto unknown differences in exposure to nickel between the Federal Republic of Germany and other countries.

Approximately two thirds of the nickel patients are females. This preponderance may be a consequence of peculiarities of female skin metabolism or it may be connected with a greater relative exposure to nickel by females. In former years extensive exposure to nickel by females could perhaps be ascribed to garment appliances and to non-precious ornaments. Long lasting contact with nickel metal brought about by rubbing action on a possibly sweating skin incited in many cases nickel hypersensitivity; only secondarily a nickel contact eczema manifested itself on the hands (7). Nowadays garment appliances are, however, coated with or being replaced by plastic material and the primary localization of the eczema has generally changed to the hands. To appreciate this hand localization it is recalled that in non-occupational every-day life there may be two principal sources of nickel: (i) nickel commodities and (ii) nickel containing detergent solutions.

(i) In recent years American-style stainless steel kitchens have become popular in the Netherlands resulting in a change of hand contact from ceramics and aluminium to nickel-plated commodities. This increase of the use of nickel in the Netherlands is similar to that in other Western countries. It is estimated that the overall use of nickel has increased by about 10 % per year (15). Coins are also among new nickel commodities. Dutch housewives are far more frequently exposed to hand contact with coins than family fathers who generally use money orders for payments. In 1958 Samitz and Pomerantz (17) demonstrated nickel leaching from American coins by the action of sweat or by sweat in combination with sodium lauryl sulfate, the range being from 1 : 1000 to 1 : 100 (equalling to about 20,000 μM Ni^{++}/l sweat).[1] Positive results by patch testing with coins were observed

[1] Usually in patch testing a 2 % or 5 % nickel sulfate solution in water is applied ($NiSO \cdot 6\,H_2O$). The nickel ion concentration of these solutions is 0.45 % Ni = 76,000 μM/l, respectively 1.1 % Ni = 190,000 μM/l. The unit of concentration: μM/l = 10^{-6} Mol/l is preferred in order to make comparison possible between various nickel containing salts commonly used in patch testing and to appraise the lower concentrations referred to in this paper.

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Table 1. *The occurrence of nickel sensitivity among contact allergic patients at the dermatological policlinic, University of Nijmegen, before and after the addition of 0.2 % EDTA to most commercial synthetic detergent powders in the Netherlands*

Year	Total number of patients tested	Nickel sensitive patients			Percentage of housewives of the nickel sensitive patients
		Number		Percentage	
1962	507	20	=	4.0 %	70 %
1963	517	35	=	6.8 %	77 %
1964	609	42	=	6.9 %	67 %
		EDTA supplied			
1965	720	55	=	7.6 %	64 %
1966	458	41	=	9.0 %	71 %
1967 (Jan.–July)	340	22	=	6.5 %	59 %

(14, 21). This is not surprising because Everall *et al.* (5) estimated the threshold patch testing concentration at about the same level, namely 20,000 μM Ni^{++}/l; Kvorning and Svendsen (8) found positive patch tests using concentrations as low as 3000 μM/l and—when a detergent had been added—as low as 230 μM/l. There is a considerable difference, however, between a patch testing exposure (contact with a superhydrated skin for at least 24 hours) and exposure to nickel in metal form in every-day life—when the skin is not superhydrated and the contact is only ephemeral. In females there are two main occupations which give rise to a rather continuous contact with nickel during several hours per day: the cashier (coins) and the cook (stainless steel kitchen). Such occupational exposures might compete with the exposure in a normal patch test. Generally, contact with nickel in metal form may not be considered to represent sufficient exposure to lead to recurrences, but there may be some doubt about the correctness of this view.

(ii) The second important source of nickel contact is detergent solutions containing nickel. Their pathogenic role has been suggested by some (7, 11, 16, 19), but doubted by others (22). The preponderance of women with nickel contact eczema may be ascribed to the frequency of contact with such detergents. In the Netherlands 2–9 ppm nickel was found in a number of detergents (11). In Switzerland (7), Spain (16), and Ireland (4) similar amounts have been found. The suds contain 0.2–0.8 μM Ni/l. This is a low concentration compared to the estimated threshold patch testing concentration of about 200 μM/l. Some (20), however, discuss the possibility of nickel ion accumulation on the skin surface; according to others (3) this does not occur. Certainly, care should be exercised in drawing conclusions from comparison between threshold patch testing concentrations and actual environmental exposures but we wish to discuss in the following some relevant aspects in detail.

I. Eliciting Threshold, Eliciting Safety Limit and Sensitizing Safety Limit of the Nickel Concentration

Patch testing is hardly an accurate method to determine the eliciting threshold of the nickel concentration. This threshold is defined as the lowest concentration capable of causing a minimal response, clinically discernable, after a given exposure (as comparable as possible to everyday-life circumstances) in highly sensitized humans. It is of practical importance to know this concentration in an individual or in groups of persons because on this level depends the tolerance to possible future exposures (assuming that the degree of sensitization remains unchanged). A cuptest (10) is a better imitation of real-life circumstances than the patch test, although the exposure time of 6 hours is rather long as compared with reality. On the other hand it may be important that detergent suds in contact with the skin will have a higher temperature.

Two of the three hypersensitive patients investigated by Malten *et al.* (10) showed a delayed skin reaction after exposure to 1000 μM Ni/l. The third patient was very nickel-hypersensitive and showed a strong reaction when exposed to as little as 200 μm Ni/l (she also had recurrence of eczema after knitting for a quarter of an hour with nickel needles). In the cup test the eliciting threshold concentrations of nickel appeared to be in the range of 100 μM/l. In a large number of hypersensitive patients some have a still lower threshold (see e.g. 8). The true threshold concentration at which not even the most sensitized patient will show any reaction in a 6 hours cup test is estimated at 10 μM Ni^{++}/l: the *eliciting threshold concentration of nickel.*

The cup tests were performed on clinically healthy skin on the volar aspects of the forearms. In real-life circumstances, however, the condition of the skin may be unfavourably affected by environmental physical and chemical factors. Moreover, repeated contact with suds may impose and maintain an altered ion "climate" on the skin surface [dissolution of calcium (10)] and may to some extent denature skin proteins so that their binding capacities change unfavourably (3, 9). Therefore a low "safe" nickel concentration must be assumed, below the eliciting nickel threshold of 10 μM/l. We have allowed a tenth of this concentration to be considered a safe environmental concentration for nickel contact hypersensitive patients. Thus, 1 μM Ni^{++}/l (corresponding to a 0.00002 % nickel sulfate solution) is provisionally considered to be the *eliciting safety limit concentration of nickel*. This approximates the nickel content of suds as used in the Netherlands (0.2–0.8 μM Ni/l).

The above considerations concern actual patients. More important would be knowledge of nickel concentrations sufficiently low to be tolerated by healthy people and without entailing the risk of sensitization even after long and extensive contact: the *sensitizing safety limit concentration of nickel.*

In the development of any contact sensitization we deal with two groups of factors: (i) those governing the penetration of the agent through the skin and (ii) those governing the reaction of the individual after introduction of the agent. Present knowledge is insufficient to quantitate the latter, but for the time being we can only explore the first group of factors. In this respect it is important for our considerations that effective penetration will not occur when the "outside" concentration of nickel is lower than the "inside" concentration.

Herring *et al.* (6) determined the normal nickel concentration of erythrocytes to be 0.84 μM/l and of plasma 0.98 μM/l. If 1 μM/l is the "inside" nickel concentration, it may be said that a lower "outside" nickel concentration would hardly penetrate the skin effectively unless other factors such as accumulation, synergism or unknown factors (e.g. damaging influence of the vehicle on cell membranes) would play a role. For the time being it is considered—as a working hypothesis—that a concentration of about 1 μM Ni/l is the *sensitizing safety limit concentration of nickel ions.*

II. The Role of Environmental Nickel in Contact Hypersensitivity

In considering the relative importance of environmental exposures to nickel it is held that:

(i) for detergent solutions in the Netherlands a content of 2–9 ppm in commercial detergent powders results in concentrations of 0.2–0.8 μM Ni/l in the suds and this is not likely to be harmful. When properly used the suds always contain less than the sensitizing safety limit concentration of nickel (1 μM Ni/l).

(ii) continuous contact with coins and nickel plated commodities (resulting in concentrations of 20,000 μM Ni/l) gives rise to potentially dangerous exposures since this is 20,000 fold the estimated provisional eliciting and sensitizing safety limit concentration of nickel and 2000 fold its eliciting threshold concentration. We, therefore, regret the forthcoming introduction of more nickel coins in the Netherlands as well as the almost ubiquitous availability of nickel commodities in general.

Before the investigations reported by Malten *et al.* (10) we already considered the role of nickel to be important. We called on a leading detergent manufacturer in the Netherlands to keep in mind the hazards of actual or prospective nickel hypersensitive persons. We based ourselves in part on the views of Kroepfli and Schuppli (7) who considered that the secondary hand localization of nickel suspender hypersensitive women arose from contact with nickel in detergents. We found the company willing to add a surplus of 0.2 % ethylenediaminetetraacetate (EDTA) to its detergent powders as of January 1965. This surplus of EDTA was calculated to be sufficient to keep all nickel sequestered even under unfavourable situations (10). The complex constant of copper and iron EDTA are of the same order of magnitude as the complex constant of nickel EDTA (13). Moreover, the surplus EDTA will bind these ions in the tap water and also eventually the nickel leached from pans and other ware. Furthermore, the surplus EDTA will possibly reduce cumulated nickel on the epidermis originating from other contacts (20). It was hoped that by this procedure these additional sources of nickel exposure by the female population would be minimized. It may at present be estimated (10)—also in accordance with our working hypothesis—that the nickel concentration of 0.2–0.8 μM/l in the suds is not harmful in itself since this concentration would not suffice to incite nickel hypersensitivity. This statement needs, however, further clinical support. Also, the detergent exposure might eventually represent "the drop causing the container to overflow" in highly sensitized individuals or in people strongly exposed to nickel in metallic form, although no scientific evidence has so far been produced in this regard. We have endeavored to obtain some information concerning the probability of such an event occurring by reviewing statistically the incidence of nickel hypersensitivity at our clinic (table 1).

Following the introduction of EDTA in commercial detergent powders one would have expected a decrease in the number of nickel contact hypersensitive females. However, the results in table 1, covering a selected clinic population, show only a feeble decrease in the percentage of female nickel hypersensitivities. This observation gives rise to several considerations: 1) The original nickel concentration of the detergent powders did not incite nickel hypersensitivity and the addition of EDTA was unnecessary. 2) The addition of EDTA only protects the most hypersensitive patients and these will represent a small number. 3) The increasing use of nickel commodities (10 % per year) (15) causes a balance between the decrease of exposure to nickel originating from detergents and the increase of exposure due to an overall increasing use of nickel ware. If the last consideration is correct, the mentioned balance will in subsequent years become unfavourable.

To appraise further the factors affecting the incidence of nickel hypersensitivity a comparative epidemiological study is planned in cooperation with investigators in the Federal Republic of Germany where a low incidence of nickel hypersensitivity has been observed. Such a study is underway in the frame of the European Contact Dermatitis Research Committee.

SUMMARY

1) The eliciting safety limit of nickel sulfate—that is the nickel concentration which does not result in a contact allergic reaction even in highly sensitized persons—is believed to be in the range of 1 μM Ni/l.
2) The sensitizing safety limit of nickel sulfate—that is the nickel concentration which will not sensitize any exposed human being—is assumed to be about same, namely 1 μM Ni/l.

3) Commercially available detergent household powders in the Netherlands contain 2–9 ppm Ni. This content represents 0.2–0.8 μM Ni/l in the suds, which is below the eliciting and sensitizing safety limits.
4) About 0.2 % EDTA has been added to most commercially available household detergent powders in the Netherlands since January 1965. No decrease in the percentage of nickel contact allergic reactions was observed in subsequent patch testing of patients at the dermatological clinic, Nijmegen University, the Netherlands. There is no definite evidence that the percentage of females in the total group of nickel hypersensitive patients is declining. It is discussed that other factors, i.a. the contact with nickel commodities and coins may play a more important role than contact with nickel containing suds (without EDTA).
5) Since the nickel content in coins and commodities as well as nickel alloys may play a role in nickel hypersensitivity and since these aspects are essentially different in some products in the Federal Republic of Germany and the Netherlands a comparative epidemiological investigation is planned in the frame of the European Contact Dermatitis Research Committee.

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