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NICKEL SENSITIZATION AND DETERGENTS

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Nickel was found in amounts up to 9 mg/kg in several phosphate-containing detergents marketed in the Netherlands (5). In attempts to identify the cause of the Ni-sensitization, even such small quantities must not be overlooked. The easiest way to eliminate a possible Ni-sensitization caused by washing agents would be the production of Ni-free powders. The triphosphates used in the powders contain between 10 and 60 mg/kg Ni. Only phosphates made from "molecular phosphorus" contain less than 1 mg/kg. It is not possible, however, to use exclusively these phosphates in washing powders. Therefore, the only way to prevent Ni-sensitization is to find a sequestering agent for the Ni-ions, provided that the complex formed has no sensitizing properties. The sequestering agent should have a higher complex constant for Ni than for Ca and Mg.

In this study the use of ethylenediaminetetraacetic acid (EDTA) as a complexing agent and the clinical determination of the sensitizing properties of the Ni-EDTA-complex are described.

Theoretical Considerations

Ca and Mg-complexes of triphosphates are more stable (6) than the Ni-complex. This means that in solution triphosphate will first bind the Ca and Mg-ions. Then, if enough triphosphate is still available, the Ni-ions will be sequestered. If Ca and Mg-ions are added to a Ni-triphosphate-containing solution, cations will be exchanged so that Ni-ions are liberated in the solution.

Housewives with sensitive hands are generally inclined to use an underdose of the washing powder. Consequently, not only are the Ca and Mg-ions partly sequestered but also all Ni-ions remain in the solution. If Ni in the washing agent is responsible for the sensitization, we doubt if the harmful effect will be prevented even when the correct dose of washing powder is applied. In the latter case the small amount of washing solution taken up by the skin contains Ni complexed with triphosphate. However, the Ca in the upper layer of the skin will then be exchanged with the Ni, again liberating free Ni-ions.

If a surplus quantity of chelating agents is added to provide protection, this agent must have a higher complexing capacity for Ni than for Ca and Mg. The EDTA complex constant for Ni is 18 and for Ca and Mg about 10, hence this agent meets the requirement. In tap water and washing powders, however, also Cu and Fe-ions are present. Their complex constants for EDTA are of the same order of magnitude as that of Ni. To ensure that all Ni-ions are complexed so much EDTA must be incorporated in the powders that Cu and Fe are bound as well. The required amount of EDTA can be calculated to be 0.2 %.

Clinical Test

Method

The effect of exposure of the skin to compounds is normally studied by means of

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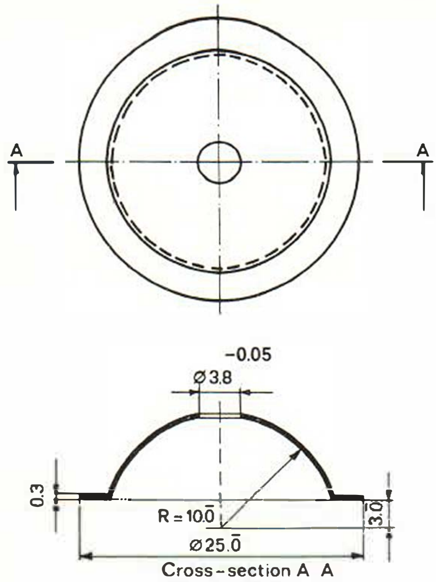

Fig. 1. Test cup.

patch tests. For testing washing solutions, however, there are some objections to this technique. First of all, it is important to get an idea of the actual concentration of the compounds in contact with the skin; during application this concentration will change as a result of evaporation of the solvent and penetration in the skin. Secondly, interactions of the investigated compound with the cotton patch are possible. Finally, in actual practice the skin is in contact with a solution and not with a compound on a fabric. For these reasons a cup test is to be preferred.

Cups of polystyrene (Fig. 1) are used in our test. A solution of resin (*Nobecutan*[1]) is poured on the bottom of an inverted 500 ml bekaer and the rim of the cup is dipped into this small amount of cement. In this way, the *Nobecutan* is applied only to the rim of the cup. The cup is slightly pressed on to the skin for a few minutes. Through the hole in the top the cup is then filled with the desired solution—after which it is closed with a small rubber stopper.

An advantage of this cup test is the possibility to analyse the contents of the cup after the experiment.

[1] AB Bofors, Nobelkrut, Sweden.

Test solutions

In view of the solubility of the Ni-complexes the highest concentration of Ni that can be studied is 25×10^{-3} M. In our investigation concentrations of 0.2×10^{-3}, 1×10^{-3} and 5×10^{-3} M $NiSO_4$ (analytical grade, containing less than 5 mg/kg Co) were chosen, depending on the sensitivity of the subjects. For each subject the minimum Ni-concentration which still gave a reaction was estimated from a preliminary screening, which also included blanks of the other reagents used. None of these gave a skin reaction of its own. In the experiments both the minimum Ni-concentration and a five times higher concentration were applied. A detergent concentration of 1 g/l DOBS JN (straight-chain dodecylbenzene sulfonate) or nonylphenol-ethylene oxide (EO) condensate (mean number of 18 EO-groups per molecule) and a triphosphate concentration of 5×10^{-3} M were used. In one series of experiments with a Ni-concentration higher than 5×10^{-3} M the triphosphate concentration was increased to the equivalent molar value. The EDTA-concentration was always molar equivalent to the Ni-content.

Results

The test solutions were applied to the volar side of the arms of three nickel-sensitive subjects for 6 hours. After 24 and 48 hours the reaction was observed and coded in the normal way (÷ is negative, + to ++++ is positive to strong positive reaction).

The results (Table 1) show that EDTA inhibits the sensitizing effect of nickel in most cases. Only the positive effect of Ni in the presence of EDTA on subject J is not clear, because at a five times higher concentration the effect is negative.

Analysis of solutions after the experiments

After the experiment the contents of the cups were removed as nearly quantitatively as possible and analysed for their Ni- and Ca-content. In Fig. 2 the Ni-concentration has been plotted as a percentage of the original concentration. Solutions 2 and 3

Table 1. *Sensitivity of three subjects to Ni-containing solutions*

Subject	B				K				J			
Nickel concentration in test solution (10^{-3}M)	1		5		1		5		0.2		1	
Read after (h)	24	48	24	48	24	48	24	48	24	48	24	48
Ni	±	+++	±	++	+	++	+	+	++	+++	+	+++
Ni+triphosphate	++	++	+++	+++	±	±	±	+	++	+++	+	+++
Ni+DOBS JN	+	+++	+	+++	+	+	+	++	++	+++	++	+++
Ni+DOBS JN+ nonphenol-18-EO	+++	+++	+++	+++	+	++	+	++	++	+++	++	+++
Ni+triphosphate+ nonylphenol-18-EO	leak	leak	+++	+++	±	+	leak	leak	++	+++	++	+++
Ni+triphosphate+ DOBS JN+nonyl- phenol-18-EO	++	+++	±	+++	+	+	±	+	++	+++	+++	+++
Ni+EDTA	–	–	–	–	–	–	–	–	leak	leak	–	–
Ni+triphosphate+ DOBS JN+nonyl- phenol-18-EO+EDTA	–	–	–	–	–	–	–	–	+	+++	–	–

show a significantly greater decrease in Ni-content than the other solutions, which means a greater Ni-absorption by the skin. Addition of other detergent components reduces this effect to the level of the original Ni-solution.

In Table 2 the relationship between the Ca-content and the original Ni-concentration is shown. As no Ca was present in the solutions before the experiments, these amounts of Ca must have been solubilized from the skin surface. The higher the original Ni-concentration, the more Ca is found in the solutions afterwards.

Discussion

From the results in Table 1 its is sufficiently clear that the Ni present is fully complexed by EDTA; the resultant complex cannot elicit any reaction in sensitized subjects.

Table 2. *Relationship between Ca-content of solution after the experiment and the original Ni-concentration*

Ni-concentration (10^{-3} M)	Ca-concentration (10^{-3} M)
1	0.17–0.27
5	0.44–1.0
25	1.4

This is in agreement with data in the literature (1–3, 7).

The Ni-concentrations used in these experiments were high as compared with the Ni-concentration in washing agents (2–9 mg/kg corresponding with 0.2–0.8 μM per l washing solution). These high concentrations were necessary to elicit a reaction within the duration of an experiment (6 hours). It would not be correct to assume that the absence of reactions at concentrations below the individual minimum indicates that also in prolonged experiments no reaction would occur. Effects such as specific absorption, cumulative binding to skin proteins and formation of insoluble compounds are only of minor importance in a short experiment. The only conclusion that may be drawn from our experiments is that the Ni-reaction is inhibited by addition of EDTA.

Since the introduction of EDTA into washing powders the number of cases of contact hypersensitivity observed at the Dermatological Department of the Nijmegen University has not decreased (4). This argues against the assumption that nickel in washing powders is the cause of nickel allergy. This means that our search must be directed towards other sources of Ni. In this respect particularly the Ni-alloys

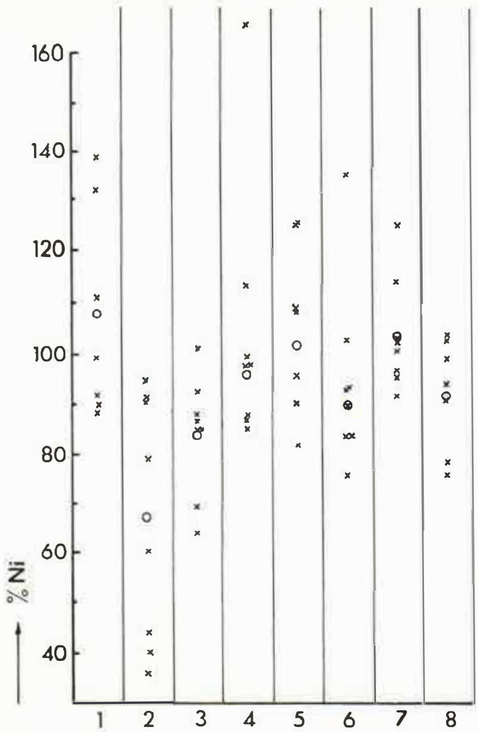

Fig. 2. Nickel contents of the test solutions after the experiment (in % of the original content).

x Values found from analysis
o Mean values

Solutions:

(1) $NiSO_4$-solution
(2) (1)+DOBS JN
(3) (2)+nonylphenol-EO-condensate
(4) (1)+phosphate
(5) (4)+DOBS JN
(6) (5)+nonylphenol-EO-condensate
(7) (6)+EDTA
(8) (1)+EDTA

used in daily life should not be overlooked. Therefore a comparative statistical investigation over a wider geographical area of the influence of nickel-plated articles in daily use has now been started.

SUMMARY

To eliminate a possible sensitization by nickel originating from detergents, ethylenediaminetetraacetic acid (EDTA) was added during the detergent manufacturing process. By clinical experiments it has been shown that the nickel-EDTA complex has no sensitizing properties. From the experiment a relationship between the reactivity of nickel and the presence of various detergent components could be established.

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