

Review Article

Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium

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The transition metals nickel (Ni), chromium (Cr) and cobalt (Co) are common causes of allergic contact dermatitis (ACD). Given the high frequency with which these allergens can be associated with hand eczema in those responsible for domestic work, it has been suggested that contamination of household consumer products with these metals may be of relevance to the causation/chronicity of hand dermatitis. Dose–response studies using 48 h occlusive patch test conditions in sensitized individuals show that $\geq 90\%$ of sensitized patients fail to react below 1 p.p.m., even on irritated skin. Assessment under more realistic exposure conditions has shown that in the presence of irritants and/or following repeated exposures, such individuals rarely react to levels below 10 p.p.m. On the basis of this information, it was recommended a decade ago that household (and other consumer) products should not contain more than 5 p.p.m. of each of Ni, Cr or Co and that, for an even greater degree of protection, the ultimate target level should be 1 p.p.m. The data generated since the original recommendations were made serve to reinforce the validity of these recommendations. Indeed, it is our view that typically the level of each of these transition metals should not normally exceed 1 p.p.m. Then, where consumer products meet this guideline fully, modern quantitative risk assessment shows clearly that elicitation of ACD is highly improbable, and the chance of the induction of sensitization is even lower.

Key words: nickel; chromate; cobalt; thresholds; consumer products; elicitation. © Blackwell Munksgaard, 2003.

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Some 10 years ago, the possibility that traces of the allergenic transition metals, nickel (Ni), chromium (Cr) and cobalt (Co), present as contaminants in household products might give rise to allergic contact dermatitis (ACD) was raised (1, 2) and then extensively reviewed (3). At that time, it was concluded that the risk of the induction of sensitization was negligible and the risk of elicitation in presensitized individuals was acceptably low, as long as the level of contamination was kept to very low levels: 'It is recommended that, for consumer products, current good practice which ensures Ni, Co and Cr contamination is less than 5 p.p.m. of each metal is an acceptable standard. To minimize the risk for very sensitive individuals (4), and when and where standardized analytical techniques permit, it is recommended that the ultimate target should be not more than 1 p.p.m. of each metal in consumer products.'

Since that publication, several new pieces of information have become available. Firstly, an interlaboratory study in Italy of housewives' eczema showed no relationship of this disease to transition metal allergy (5, 6). In addition, new dose–response data which aid our understanding of elicitation thresholds in sensitized individuals have been published and have further information on the levels of product contamination with additional commentary on the possibility that trace levels of Ni, Cr and Co might play a role in ACD (and in particular in the chronicity of some hand eczemas) has been presented. Finally, now there are sophisticated approaches to the quantification of the risk associated with skin sensitizing substances. As a consequence, it is timely to review the 10-year-old position stated at the end of the paragraph above and to examine whether it is still valid in the light of

this additional knowledge – such is the purpose of this paper.

Consumer product levels of Ni, Cr and Co – the challenge

In the earlier work (1–3), the evidence that these allergenic transition metals could cause ACD, particularly from their presence at relatively low levels in consumer products, was considered and led to the conclusion that they did not. Although not stated explicitly, it is clear that a level of 100 p.p.m. or more was an unacceptable risk. Since then, further evidence in support of this has been presented; Ingber and colleagues (7) showed about 100 p.p.m. of Cr in household products and associated it with the high incidence of positive patch test reactions to this allergen in Israel. Other workers (8) similarly have noted the potential association between hand eczema and Cr sensitivity. Most recently, a group working in northern Italy (9) has noted a possible weak association between the risk of sensitization to Co and use of fabric washing powders. This work generated considerable publicity in Italy and generated both debate by representatives of Italian Workers Union (ISPESL) and a more formal reaction (10, 11). As well as the public reaction (presented at the 6th Congress of the European Society of Contact Dermatitis), work was also undertaken to measure the levels of Ni, Cr and Co in a range of consumer products taken off supermarket shelves, effectively checking in a random way whether the policy above was being adhered to. Table 1 presents the results of an independent analysis of household consumer products in Italy and indeed confirms that the levels of transition metals were well within the 1993 recommendation. Additionally, a recent survey of 95 detergent products by the Dutch authorities showed that approximately 90% contained <1 p.p.m. of Ni, Cr or Co; all were well below 5 p.p.m. (12). In those products which contained detectable levels of these transition metals, the average levels were

0.45 p.p.m. Ni, 0.64 p.p.m. Cr and for Co the highest level was 0.28 p.p.m. Nevertheless, the challenge posed to manufacturers of consumer products concerns the need to address the 10-year-old recommendation noted above. Is it still valid? Should it be republicized and/or strengthened?

Thresholds for Ni, Cr and Co in humans

The argument that thresholds do indeed exist, both for the induction and the elicitation of ACD, has been expounded recently, from both theoretical and practical perspectives (13–15). Importantly, however, since the publication in 1993 (3), several practical studies have been undertaken which have examined in considerable detail thresholds for the elicitation of ACD to Ni, Cr and Co. It should be noted here that it is the view of the authors that thresholds for elicitation in sensitized individuals are always the same or lower than the threshold for the primary induction of sensitization; therefore, what is safe for elicitation, by definition, is safe with respect to induction.

One criticism which can be applied to threshold dose–response studies for contact allergens is that of skin site: studies done on the back or the arm may be misleading for the hand, which is typically the skin site with chronic eczema. A small study addressing this challenge was conducted and demonstrated that in reality the threshold on the hands of Ni-allergic volunteers with hand eczema was no different to that at other skin sites (16).

More recently, patch test dose–responses and repeated open application test dose–responses were carried out in a series of Cr-allergic volunteers in Israel (17). This investigation served to demonstrate that, as had been concluded earlier, the threshold for the elicitation of Cr allergy in skin was likely to be in the region of 1 p.p.m., even where the skin contact was repeated and performed in the presence of an irritant substance.

Table 1. Analysis of levels of Ni, Cr and Co in selected current consumer products

Product type (number)	Ni (p.p.m.)	Cr (p.p.m.)	Co (p.p.m.)
Heavy duty powders (<i>n</i> = 9)	0.5	1.1	0.1
Hand wash powders (<i>n</i> = 4)	0.9	0.9	0.1
Laundry tablets (<i>n</i> = 3)	0.5	0.6	0.2
Heavy duty liquids (<i>n</i> = 9)	0.1	0.1	0.1
Machine/hand wash liquids (<i>n</i> = 4)	0.1	0.2	0.1
Hand wash liquids (<i>n</i> = 4)	0.1	0.1	0.1
Fine wash liquids (<i>n</i> = 2)	0.1	0.2	0.1
Dishwashing liquids (<i>n</i> = 9)	0.1	0.1	0.1
Liquid/powder cleaners (<i>n</i> = 6)	0.4	0.4	0.1

Data courtesy of Stazione Sperimentale Oli & Grassi.

The largest series of threshold studies of transition metal allergy in recent years, however, is those conducted in Denmark. Initial investigation indicated that the threshold for Ni reactivity on unoccluded skin was >100 p.p.m. (18). Menné and colleagues (19) adapted and extended an approach described for Ni allergy so that a detailed study of elicitation thresholds was possible in transition metal allergic volunteers with existing hand eczema. In their work with Ni (20), it was demonstrated that the threshold for elicitation was between 10 and 100 p.p.m., even after several weeks of repeated daily exposure. Such a result was in line with the earlier study indicating the hand was similarly sensitive to other body sites (16). The conclusions from this work and earlier studies were also supported by further recent data examining the impact of the anionic surfactant sodium lauryl sulphate on the elicitation dose-response to Ni (21). Subsequently, Menné's group (22) evaluated the effects of daily repeated exposure to low Co or Cr concentrations on the hands of patients with Co or Cr allergies. Repetitive daily exposure to 10, 50, 100 or 200 p.p.m. Co, or 10 and 100 p.p.m. Cr elicited a hand eczema only in the Cr-sensitive patients.

Another study by Nethercott et al. (23) demonstrated a minimum eliciting threshold for Cr^{6+} of $0.018 \mu\text{g}/\text{cm}^2$ (approximately 2 p.p.m.) for 1 out of 59 patients and a 10% minimum elicitation threshold of $0.089 \mu\text{g}/\text{cm}^2$ (approximately 10 p.p.m.). It is worth noting that these authors presented their skin contact dose in terms of dose per unit area, which is certainly the most appropriate form, being scientifically the most relevant, permitting more ready inter-experimental comparisons to be made. All the studies on Cr have been carefully reviewed recently (24).

Risk assessment – induction

In the previous publication on acceptable levels of Ni, Cr and Co (3), the assessment of the risk presented was based upon a comparative evaluation, an approach both typical of the time and still common today. Essentially, the likelihood that the allergen will (or will not) either induce or elicit skin sensitization is judged by comparison with other known allergens applied in similar use situations. Implicit in this is that the allergens being considered are well understood in terms of their relative potency, and because they are being considered in the context of the same exposure, safety judgements can be made (25). More recently, however, a newer strategy for skin sensitization risk assessment has been expounded

(26, 27). This approach gives a semi-quantitative view of risk, focusing on the methods of risk assessment more generally applied to other toxicological endpoints (28, 29). Specifically, by estimating the exposure to the allergen and its allergenic potency, it is feasible to assess semi-quantitatively the sensitization risk of an ingredient or a contaminant in a particular product type. Key steps of the risk assessment process are establishment of human exposure (in $\mu\text{g}/\text{cm}^2$), known safe benchmarks (NOEL), uncertainty factors (UF), the acceptable dermal exposure level (sensitization reference dose S-Rfd) and a comparison of the consumer exposure to the acceptable exposure level. In the following section, we demonstrate the principle of the exposure-based risk assessment, as it has been previously shown for beauty care products (28), but for a laundry detergent contaminated with 1 p.p.m. of Cr (selected as a model for the other transition metal allergens and, in our view, likely to be the most potent). We calculate the anticipated consumer exposure and compare it with the acceptable dermal exposure for induction and elicitation of ACD to Cr. Note that it is assumed that all Cr is present as Cr^{6+} , which is the form of Cr known to be associated most strongly with skin sensitization (30).

Dermal exposure to Cr can occur from hand laundry and fabric wearing. It is common that laundry is washed by hand, and it results in direct contact of detergent solutions with skin of hands and forearms. There is the potential for ingredients or impurities to leave residues on the clothing after washing, and consequently, wearing the clothes results in contact, albeit almost negligible, to certain ingredients or impurities, e.g. Cr. Additionally, clothing stains are spot-treated by hand with detergent. If a powdered detergent is used, a paste of about 50% (AISE standard value) will be used or a liquid will be applied directly. As the exposed skin surface during pretreatment is very limited, hands are usually washed after the task, and the duration of the task is very short; the anticipated exposure will be much less than that from hand washing of laundry. The pretreatment scenario will, hence, not be presented below.

Establishment of human exposure

Direct skin contact from hand laundry

The contact time with ingredients during hand washing is short (approximately 10 min) (31) and the amount of product on skin is very low. The following worst case assumptions should address this scenario:

(1) Highest concentration of laundry detergent in hand washing solution is approximately 1% (10 mg/ml) (31).

(2) Highest concentration of Cr in a laundry detergent is 1 p.p.m. (target limit in reference 3).

(3) Assuming a film thickness of 100 μm (0.01 cm) (32) on the hands, a 100% transfer from medium to skin and 100% remaining on skin (i.e. assuming no rinsing).

(4) The duration of the procedure is not taken into account in the calculation, as we already assume 100% remains on skin. In addition, the time of exposure will be considered indirectly in the use-pattern uncertainty factor (see below).

General equation for dermal exposure from hand laundry:

$$\text{Exposure} = F1 \times C' \times F2 \times F3,$$

where $F1 = 0.000001$ (weight fraction of substance in product = 1 p.p.m.), $C' = C \times T_{\text{der}}$ (product load in mg/cm^2), $C = 10 \text{ mg}/\text{cm}^3$ (i.e. 1%, the product use concentration), $T_{\text{der}} = 0.01 \text{ cm}$ (thickness of the aqueous layer in contact with skin), $F2 = 1$ (weight fraction transferred from medium to skin = 100%), $F3 = 1$ (weight fraction remaining on skin = 100%).

Based on the above calculation, skin exposure = $0.0001 \mu\text{g}/\text{cm}^2 \text{ Cr}$.

Indirect skin contact from wearing clothes

Residues of components or contaminants of laundry detergents may remain on textiles after washing and could come in contact with the skin via transfer from textile to skin. In our example, the amount of Cr deposited on the fabric is estimated using these assumptions:

(1) Typical amount of laundry detergent used is 150 g (0.15 kg) and a typical total weight of fabric load in the washing machine is 3.5 kg (31).

(2) The fraction of substance deposited on fabric is 2.5%. This is based on a water consumption of 60 l in the washing machine (15 l in the main wash and 45 l in the rinsing cycle) and an intermediate spinning cycle between the first and the second rinse. A final water concentration of 2.5% is calculated (33).

(3) The fabric density is estimated to be $10 \text{ mg}/\text{cm}^2$ which represents mixed fabrics (cotton and others).

(4) 1% transfer from fabric to skin with 100% of material transferred remaining on skin (34).

(5) The duration of the procedure is not taken into account in the calculation, as we already assume 100% remains on skin. In addition, the time of exposure will be considered indirectly in the use-pattern uncertainty factor (see below).

General equation for dermal exposure:

$$\text{Exposure} = F1 \times C' \times F2 \times F3,$$

where $F1 = 0.000001$ (weight fraction of substance in product = 1 p.p.m.), $C' = M_p \times F' \times FD1/W1$, $M_p = 0.15 \text{ kg}$ (amount of product used), $F' = 0.025$ (weight fraction deposited on fabric), $FD1 = 10 \text{ mg}/\text{cm}^2$ (fabric density), $W1 = 3.5 \text{ kg}$ (total machine load), $F2 = 0.01$ (weight fraction transferred from fabric to skin), $F3 = 1$ (weight fraction remaining on skin).

Based on the above, exposure = $0.0000001 \mu\text{g}/\text{cm}^2 \text{ Cr}$.

Determination of known benchmarks/NOEL

The contact sensitization potential for Cr has been established by a number of LLNA assays in different laboratories (35). The experimental results and the resulting EC3 values were very consistent. Based on these studies and the reported relationship between EC3 and NOELs (36), a specific human NOEL for Cr was estimated:

$$\text{NOEL } K_2Cr_2O_7 \text{ (LLNA data)} = 14.5 \mu\text{g}/\text{cm}^2 \text{ (EC3 = 0.058\%)} = 5.12 \mu\text{g}/\text{cm}^2 \text{ expressed as Cr}$$

Chemicals with NOELs between $1\text{--}10 \mu\text{g}/\text{cm}^2$ derived from LLNA data have been grouped and a conservative NOEL of $1 \mu\text{g}/\text{cm}^2$ is often assumed for that class (36). In line with that the NOEL for Cr is equal $1 \mu\text{g}/\text{cm}^2$.

Determination of uncertainty factors and calculation of the acceptable dermal exposure level

Uncertainty is inherent in the extrapolation process. This is acknowledged by the application of 'uncertainty factors' (UF), sufficiently conservative so as to provide confidence that the allowable human exposure will be safe (29). In extrapolating from experimental (HRIPT, LLNA or other) data, there are 3 basic areas to be considered: inter-individual response variability, product matrix differences between what was tested in the patch test (or LLNA) versus the product formulation to which the consumer will be exposed to, and variations in product usage patterns (e.g. part of the body exposed, skin integrity, occluded or non-occluded and duration of exposure), which are not addressed in the exposure assessment. The maximum uncertainty factor in these areas is 10-fold, depending on the area and conditions, factors of 1 or 3 may be appropriate. An additional uncertainty factor to account for inter-species variability is not considered as it was

shown that LLNA data correlate very well with human data (36–38).

For the Cr risk assessment the following UFs were chosen:

- (1) Inter-individual variability = 10x (to account for inherent differences between individuals.)
- (2) Product matrix effect = 3x (The Cr NOEL was derived from a LLNA in water. The laundry detergents are more complex and could have some irritating properties. An UF of 3 can be justified for a mild to slightly irritating formulation.)
- (3) Use pattern = 3x. This reflects differences in skin permeability in the LLNA and the parts of the body exposed during hand washing and fabric wearing. A factor of 10 is considered too high as exposure is normally only for brief periods of time; the higher value would be most appropriate for example in association with regular deodorant use.

Sensitization uncertainty factor (SUF) = $10 \times 3 \times 3 = 100$ (note that 3 is actually 3.16 or the half log of 10 which makes the calculation $10 \times 3.16 \times 3.16 = 100$).

The SUF are used with the default NOEL to determine the maximum human exposure limit (S-Rfd) for the substance of interest, here Cr. Simply stated, the S-Rfd for Cr in the product is equal to the NOEL divided by the SUF.

Acceptable dermal exposure level S-Rfd:

$$\text{S-Rfd} = \text{NOEL} / \text{SUF} = 0.01 \mu\text{g}/\text{cm}^2 \text{ Cr.}$$

Comparison of consumer exposure to acceptable exposure level

The anticipated consumer hand exposure from a laundry detergent ($0.0001 \mu\text{g}/\text{cm}^2$) is much lower than the acceptable dermal exposure to Cr ($0.01 \mu\text{g}/\text{cm}^2$). It suggests that the 1 p.p.m. Cr in a laundry detergent would pose essentially no sensitization risk. Indirect skin contact from wearing fabric washed with detergent results in almost negligible consumer exposure ($0.0000001 \mu\text{g}/\text{cm}^2$). It is again important to note that this is about induction of sensitization and not the elicitation reactions of previously sensitized individuals. Figure 1 clearly portrays how consumer exposure compares to acceptable exposure levels for induction.

Similar calculations can be done for other household products, e.g. liquid detergents, hand dishwashing liquids and hard surface cleaners. The exposure is anticipated to be similar to the outlined hand wash scenario. For certain products the consumer could, however, come into contact with more concentrated products. This exposure is of short time to a limited skin area, and hands are usually washed after the task. In those cases, the calculated consumer exposure

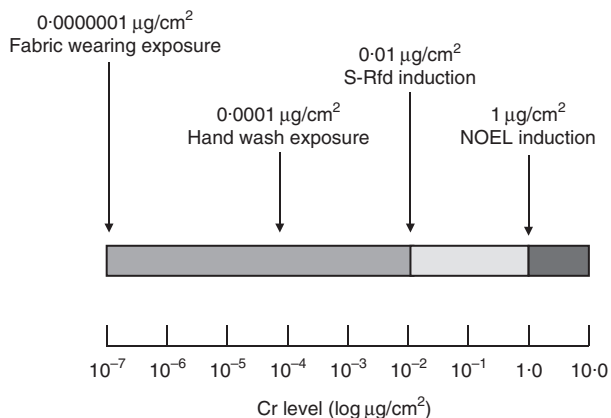


Fig. 1. Risk assessment calculations for the induction of sensitisation to Cr.

would be of the same order of magnitude as that of the acceptable sensitization reference dose (0.02 – $0.05 \mu\text{g}/\text{cm}^2$ Cr). This underlines the need to keep the levels for Cr within the agreed levels (<5 p.p.m.) with the actual target being 1 p.p.m. Note that the reality is that products normally contain <1 p.p.m. Cr (Table 1).

Risk assessment – elicitation

Although the likelihood of the induction of sensitization in fact may be improbably low, it is still reasonable to ask whether individuals who have already become sensitized via another route, e.g. individuals who have developed Ni allergy via ear piercing might react to low levels present in consumer household products. In this area, we are fortunate in having a considerable body of experimental data derived from human studies on which to base a safety assessment.

Patch test dose–responses, repeated open application test responses in Cr allergic volunteers and finger immersion test results indicate that the absolute threshold for elicitation in the most sensitive individuals and under rigorous exposure conditions is in the region of 1 p.p.m., which translates to an exposure of approximately $0.01 \mu\text{g}/\text{cm}^2$ Cr. Comparing the anticipated consumer exposure for the different laundry scenarios (see above) with this elicitation threshold, it is clear that the risk for eliciting a positive response in Cr-sensitized people is extremely low in all normal product-use situations. Where Cr contamination exceeds the guidelines and there is substantial exposure to neat product, there is a risk that the most Cr-sensitive individuals might experience an elicitation of their allergy.

As previously suggested, levels not only for Cr but also for Ni and Co need to be tightly controlled. A review of the Ni data shows that the

threshold for elicitation for the great majority of individuals is 1 p.p.m. or higher (1). More recent studies of elicitation which approach closely realistic exposure conditions in the at risk population indicate that the threshold in practice may be rather higher, in the 10–100 p.p.m. region (19). Of special note is that this work involved experimentation on the fingers of Ni-allergic volunteers with existing hand eczema. However, it should be noted that the situation mimicked was of single product exposure; in reality, there may be multiple daily exposures. Hence, there is a need for caution in the interpretation of these apparently higher thresholds. Only limited data is available on elicitation thresholds for Co (3, 22). Nevertheless, the data suggest that the risks are similar to those for Ni and Cr, possibly even lower, as Co-sensitive patients failed to react after repetitive exposure to 10, 50, 100 or 200 p.p.m. Co (22).

Conclusion

Ni, Cr and Co have, for many years, been recognized as relatively common causes of ACD. In the case of Ni and Cr, the source of the allergen can often be identified (e.g. jewellery, cement and leather); Co is a much more difficult allergen (3, 39). Given the high frequency with which these allergens can be associated with hand eczema in those responsible for domestic work, it has been suggested that contamination of household products with these transition metals may be of importance in the causation/chronicity of hand dermatitis. Dose–response studies using 48 h occlusive patch test conditions in groups of sensitized individuals show that $\geq 90\%$ of sensitized patients fail to react below 1 p.p.m., even on irritated skin. Assessment under more realistic exposure conditions has shown that in the presence of irritants and/or following repeated exposures, such individuals rarely react to levels below 10 p.p.m. On the basis of this type of information, it was recommended, almost a decade ago, that household (and other consumer) products should not contain more than 5 p.p.m. of each of Ni, Cr or Co and that for an even greater degree of protection, the ultimate target level should be 1 p.p.m. (3). We consider that the additional data collected since the original recommendations were made serve to reinforce the validity of these recommendations. Furthermore, recent legislation in the EU has proposed a limit of 2 p.p.m. Cr in cement products (40). Given these facts, it is our view that typically the level of each of these transition metals should not normally exceed 1 p.p.m. in household products. Where consumer products meet such a guideline fully, modern

quantitative risk assessment clearly shows that elicitation of ACD is highly improbable, and the chance of the induction of sensitization is even lower.

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