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**Nickel, Cobalt and Chromium
in Consumer Products:
Allergic Contact Dermatitis**

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Nickel, Cobalt and Chromium in Consumer Products: Allergic Contact Dermatitis

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Nickel, Cobalt and Chromium in Consumer Products: Allergic Contact Dermatitis

SUMMARY

Despite the improved awareness of the potential for nickel, cobalt and chromium to cause skin allergy, the incidence of sensitisation resulting from them is generally on the increase especially for nickel.

This report reviews data from the published literature and unpublished industry data on transition metal contamination of consumer products, and assesses the hazard to man. Consumer products are defined for the purposes of this report as personal care items and detergent/cleaning products used regularly in domestic work.

The analytical data demonstrate that consumer products are a relatively minor source of contact for nickel, cobalt or chromium. The trace levels of nickel, cobalt and chromium found in consumer products will not be the primary cause of sensitisation to these transition metals. Levels will be too low and exposure too brief. A person allergic to these metals has many other more significant sources of daily contact such as jewellery and metal objects. It is therefore necessary to focus on decreasing the high exposure to these transition metals from other sources rather than on possible trace amounts of metals found in consumer products.

Current good manufacturing practice ensures that nickel, cobalt and chromium concentrations in consumer products are less than 5 ppm of each metal. It is recommended that this should be accepted as a standard for maximum concentrations and that the target should be to achieve concentrations of no more than 1 ppm. Since it is recognised that consumer products manufactured to this standard are unlikely to give rise to allergic contact dermatitis, occasional minor deviations above 1 ppm are not seen as posing a significant risk. Even with the strictest controls it is recognised that some allergic individuals may show an elicited reaction. This situation is no different from that which applies to many chemicals known to elicit a reaction in exceedingly

sensitive people and to many foods known to cause problems in specific sub-populations. In all such cases the only solution is avoidance of the chemical (product) or food. In general, practical regulatory control of the use of sensitisers is aimed at the vast majority of people and not the population of sensitised individuals which is exquisitely sensitive.

1. INTRODUCTION

The transition metals nickel, cobalt and chromium are a major cause of allergic contact dermatitis in the general population (Fisher, 1986; Fowler, 1990). Recently, some groups have raised again the issue of whether trace levels of these metals in consumer products contribute to this disorder (Nava *et al*, 1987; Vilaplana *et al*, 1987; Angelini and Vena, 1989). To address this question a Task Force was convened with the following terms of reference:

to collect data on the concentrations of nickel, cobalt and chromium in consumer products and consider the forms of nickel, cobalt and chromium for which there is information on skin sensitisation;

to review the role of nickel, cobalt and chromium in the aetiology of allergic contact dermatitis in the light of the concentrations found;

to recommend an acceptable level for allergic individuals.

The definitions of the most important terms used in this report are given in Appendix 1.

2. BACKGROUND

Allergic contact dermatitis (ACD) is a relatively common skin condition which is caused by a wide range of substances eg. perfumes, preservatives, plants, dyes, rubber chemicals, resins as well as transition metals (Cronin, 1980; Fisher, 1986). Nickel (Ni), cobalt (Co) and chromium (Cr) are often associated with ACD at specific skin sites (eg. the hands) and contribute significantly to occupational disease (eg. chromium in cement). Not infrequently the dermatitis resulting from contact with these metals is chronic, even when obvious sources of exposure have been eliminated (Burrows, 1983; Angelini and Vena, 1989; Adams, 1990; Fowler, 1990; Moeller, 1990).

At a dermatology clinic, when an individual presents with possible contact dermatitis, it is common for the medical history and examination to be supplemented by patch testing (cf. Appendix 2). By this means, a fairly high incidence of allergy to the transition metals has been identified (Cronin, 1980; Fisher, 1986; Fowler, 1990). Whilst in general the source of metal contact is well known (pierced ears, metal working/refining industries, cement etc), in a minority of cases it is not possible to identify a particular source of contact with the offending metal. Although there may be no direct correlation, the frequency of association with a possibly chronic condition such as hand eczema can be high (Wilkinson and Wilkinson, 1989). This leaves the physician to search for less obvious sources of metal contact. In this manner, the problem of chromium in household bleach was first identified (Rabeau and Ukrainczyk, 1939).

Nickel, cobalt and chromium are not components of modern formulations for the consumer products in question (see below for definition), but they are present as low level impurities in some of the raw materials. Modern analytical techniques can detect trace levels (low ppm range) of these metals in various consumer products. Consequently, several authors have suspected that impurity levels of nickel, cobalt or chromium in household products, whilst not a primary cause of allergy, could be sufficient to maintain the allergic

dermatitis (Nater, 1963; Malten and Spruit, 1969; Feuerman, 1971; Nava *et al*, 1987; Vilaplana *et al*, 1987; Angelini and Vena, 1989; Kokelj *et al*, 1989).

Clearly, it is essential that individuals with an existing contact allergy to these transition metals do not suffer episodes of dermatitis as a consequence of using consumer products contaminated with nickel, cobalt or chromium. The primary induction of allergy by this route would also be unacceptable.

This report reviews the published literature and unpublished industry data on transition metal contamination of consumer products, and assesses the hazard to man. Consumer products are defined for the purposes of this report as personal care items and detergent/cleaning products used regularly in domestic work. The Task Force realised that other products may contain nickel, cobalt and chromium in variable amounts but these products would be used in only a limited way such that exposure would be negligible. The Task Force has performed a hazard/risk assessment for the transition metals. Data were collected in order to provide an accurate measure of sensitisation potential, including dose response data, in both man and animal models. This information has then been assessed in relation to levels of the transition metals found in consumer products, and in relation to the known epidemiology of allergic contact dermatitis to these metals and in the context of the nature and extent of consumer exposure.

On the basis of the information generated guidelines are recommended which should minimise consumer risk in particular to the more sensitive individuals.

3. REVIEW OF ALLERGIC CONTACT DERMATITIS RESULTING FROM EXPOSURE TO NICKEL, COBALT AND CHROMIUM

3.1. DEFINITION OF ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) or contact sensitisation is a common inflammatory skin disease caused by agents such as plants, chemical compounds and topical medications. It is defined as a delayed hypersensitivity response in a person's skin manifested as an eczematous reaction to contact between the epidermis and the sensitising agent. Several factors dictate the severity and persistence of the skin response including the sensitivity of the subject, the length of the exposure, the dose and the potency of the antigenic stimulus (Katz, 1990). The development of ACD is a two step process involving induction and elicitation. This process is described in more detail in Appendix 3.

It is necessary to distinguish between allergic and irritant skin reactions.

An **allergic** (contact sensitisation) reaction is an inflammatory reaction which is a consequence of an immunological process. It is characterised by itching, erythema, papules, oedema and possibly vesicles. The reaction boundary is often diffuse and the response usually lasts for several days. Another common feature is that the skin reaction can also increase in strength after removal of the test substance (Fregert, 1981).

An **irritant** reaction (Irritant Contact Dermatitis) is an inflammatory reaction which is provoked by direct cell damage and not by an immune process. Characteristically the erythema is limited to the damaged contact area, the reaction area being sharp. In mild, acute cases there is no itching, oedema, papules or vesicles and the erythema appears within one day and disappears rapidly after removal of the irritating substance. Some irritants can cause the skin to swell without erythema and strong irritants can produce erosions or bullae (Fregert, 1981).

It is, in practice, difficult to distinguish clinically between contact dermatitis caused by irritant and allergic reactions. Studies of healthy

individuals using patch tests may clarify whether a substance is likely to produce responses which are irritant or allergic in nature but the difficulty in diagnosis may persist due to the great variation among individuals in susceptibility to irritants (Fregert, 1981; Fowler, 1990).

3.2. ALLERGIC CONTACT DERMATITIS TO NICKEL, COBALT AND CHROMIUM IN MAN

3.2.1. Introduction

The metals nickel, cobalt and chromium are ubiquitous in the environment. Despite the improved awareness of the potential of these metals to cause skin allergy, the incidence of sensitisation resulting from contact with them is generally increasing (Fowler, 1990). The prevalence of metal allergy in the population prompts the search for metal releasing objects with which the individual comes into contact.

In this section, epidemiological and human patch test data will be considered separately. A summary of information gathered from the literature on the epidemiology of ACD to nickel, cobalt and chromium can be found in Tables 1 and 2. It must be remembered that the incidences of ACD reported almost always relate to patients attending dermatology clinics and are not representative of the general population.

3.2.2. Epidemiology

Epidemiology is the scientific discipline used to describe disease occurrence in a population and to assess the nature and distribution of risk factors. Thus, epidemiological research provides the basis for prevention of disease and planning of health care.

The prevalence of metal allergy varies with the population tested, the geographic location and patch test techniques, vehicles and concentrations employed.

3.2.2.1. Epidemiology, Nickel. Nickel is the most frequent contact allergen (Menné *et al*, 1989; and Tables 1 and 2). Although the majority of cases are non-occupational, work related nickel dermatitis is a predominant diagnosis in reports on permanent disability due to skin disease. Nickel dermatitis was first clinically recognised as "Das Galvanizierekzem" in 1889 (Blasko, 1889). Occupational nickel dermatitis was common in the 1920's and 1930's (Bulmer, 1926; Jadahssohn and Schaaf, 1929; Du Bois, 1931), while nickel dermatitis was first reported in consumers in the early 1930's and recognised as a large scale consumer problem in 1936 (Bonnevie, 1936).

The intimate contact of metallic nickel and nickel alloys with the skin is the main reason for the high incidence of nickel allergy in the population. Most cases in women are non-occupational and result from ear piercing or intimate contact with metal objects such as clips, buttons, zippers, buckles, and clasps (Peltonen and Terho, 1989; Menné *et al*, 1987; Emmet *et al*, 1988; Widstroem and Erikssohn, 1989).

Schubert *et al* (1987) stated that costume jewellery, wrist watches and metal clothing buckles are not only the most important sources of primary nickel sensitisation but also of relapses and persistence of allergy. Santucci *et al* (1989) asked 730 schoolgirls (mean age 17 years) about the incidence of contact dermatitis at the sites of direct contact with earrings, 92% regularly wore earrings, 70% daily, 17% weekly, 13% monthly; 438 girls (67%) described symptoms of itching, erythema or eczema and a clear relationship was found with the repeated use of cheap (67%), gold (2%) or silver (1%) earrings, or more than one of these. The schoolgirls were not patch tested and thus the authors could not say if they were truly sensitised.

3.2.2.2. Epidemiology, Cobalt. Cobalt is an essential trace element. It is ubiquitous in foods (Schrauzer, 1984). Many metal alloys contain cobalt together with nickel.

Cobalt is a metal which also causes allergic reactions in man (Cronin, 1980; Doods-Goossens *et al*, 1980; Fisher, 1986; Fowler, 1990; Shehade *et*

a7, 1991). The latter reported on 4,721 subjects of whom 5.7% were patch test positive to cobalt. Simultaneous allergy to nickel and cobalt is frequent and cobalt has been considered of significance in persistent hand eczema in patients with positive patch tests to nickel and cobalt (Menné, 1980).

Menné (1980) performed patch tests on 168 subjects with pure cobalt salts and few reacted. Since isolated cobalt allergy is very rare, it has been suggested that positive results could occasionally be due to nickel impurities in cobalt (Rystedt and Fischer, 1983; Fisher, 1986; Eady et al, 1991).

3.2.2.3. Epidemiology, Chromium. Chromium metal, alloys (eg. stainless steel) and chrome plating are not soluble and in this form its sensitisation potential cannot be realized. Nevertheless the corrosive action of sweat must be borne in mind as this might cause solubilisation of chromium and thus realize its potential.

The sensitising capacity of chromium salts depends on their concentration, valency, solubility, pH, and presence of organic matter. Hexavalent soluble salts in an alkaline medium have the greatest sensitising potential (Burrows, 1983) and there is a good correlation between the solubility of chromium salts and their sensitising potential.

Organic material has the ability to reduce hexa- to trivalent chromate (Burrows, 1983). Hexavalent salts, which are more soluble than trivalent salts, penetrate more easily through the skin where they are reduced to Cr^{3+} which is considered the sensitising agent (Polak, 1983).

The occurrence of chromate allergy in cement workers was first described by Bonnevie (1939) and Stauffer (1939) but was thought to be due to chromium compounds in leather gloves. Pirila and Kilpio (1949), reported that 10 patients with cement dermatitis were sensitive to chromate. Jaeger and Pelloni (1950) demonstrated that 32 patients with cement dermatitis all had a positive patch test to potassium bichromate

but of the 168 other patients with eczema from other causes, only 5% reacted. This was first proof of the relation between cement dermatitis and chromium allergy. Subsequently cement was recognised as the most common cause of primary sensitisation to chromate (Cronin, 1971, 1980). Recently there has been a decrease in the number of cases of cement dermatitis probably due to changing patterns of handling cement, such as increasing use of ready-mixed cement, increased automation in the building industry, addition of ferrous sulphate (a complexing agent for chromium) and the improved facilities for personal hygiene.

Bleaches and liquid detergents containing chromates were reported to be a cause of "housewives dermatitis" in Belgium, France, Spain and Italy. Garcia-Perez *et al* (1973) quoted a high incidence in Spain. Lachapelle *et al* (1980) showed that liquid bleach in Belgium contained up to 83 ppm (mg/l) chromate. A correlation between the use of these bleaches and the frequency of chromate allergy in Belgium was suggested (Dooms-Goossens *et al*, 1980). Lachapelle *et al* (1980) showed that removing chromate from bleaches reduced the incidence of dermatitis. In other countries bleaches had only trace levels of chromate, which were no different from other consumer products (Hostynek and Maibach, 1988).

Feuermann (1970, 1971) reported that in two groups of housewives with eczema in Israel, a high proportion (34% in 1970; 91.6% in 1971) were patch test positive to potassium bichromate. This high incidence has never been reported by others. All detergents analysed contained traces of chromates. There is no evidence that the detergents used in Israel have a higher chromate content than those used elsewhere.

In general, the problem of chromate allergy associated with household products has resulted from deliberate addition of chromate salts to the product. Cessation of this manufacturing practice resolved the outbreak of ACD (Burrows, 1983).

3.2.2.4. Incidence Trends and Sex Differences. Historically the incidence of positive patch test reactions to chromate and nickel remained remarkably constant (9% in 1937; 12% in 1970) (Baer *et al*, 1973). During the last

two decades a clear increasing trend was observed for nickel ACD and to a lesser rate for cobalt ACD, but a decreasing incidence was found to chromate (Gailhofer and Ludvan, 1987; Kiec-Swierczynska, 1990) (cf. Table 1). There are clear sex differences in the incidence of positive patch test reactions to these metals.

Nickel: Studies of the trends over a long period indicate that nickel allergy is increasing, particularly in the female population (Table 1) (Angelini and Vena, 1989; Kiec-Swierczynska, 1990).

Several studies have been conducted which examined the incidence of patch test reactions to nickel in the general female population. These have been summarised and show approximately 10% of women may have a nickel sensitivity (Menné *et al*, 1989), although the figure was only 0.67% in a group of male soldiers (Seidenari *et al*, 1990).

In all reports from dermatological departments in industrialised countries, nickel is the most frequent contact allergen. The increasing incidence has continued and in Sweden one in four women patch tested was positive to nickel (Moeller, 1990). In former times, most cases of female nickel dermatitis were ascribed to suspenders. It would be expected that changes in female clothing habits should have been followed by a marked decrease in nickel sensitisation. This has not been the case. Instead, ear piercing and the wearing of cheap jewellery have maintained the intimate metal/skin contact leading to nickel allergy. The higher frequency of nickel allergy among young girls with pierced versus non-pierced earlobes was impressive (Larsson-Stymne and Widstroem, 1985). Female reactors do not predominate in all countries, although the exposure may be the same as in Kuwait, Japan and Nigeria (Kanan, 1969; Sugai *et al*, 1979; Oluide, 1985). Local dressing habits and varying occupational exposure may explain these differences. In Nigeria, nickel plated wrist watches and watchbands are the main sources of nickel sensitisation in men. The hot and humid climate increases corrosion from nickel plated articles and alloys (Menné *et al*, 1989). Some men are increasingly decorating themselves by ear piercing and wearing jewellery, as well as being exposed to metal in jeans, etc.

This results in an increasing ACD incidence in males, but on a significantly lower level than in females (cf. Table 2).

Romaguera *et al* (1988) investigated the sources of contact allergy from nickel. They tested 964 patients who complained of metal intolerance and compared the results to those of 200 controls. The authors noted an increasing incidence of positive patch tests to nickel from 13.8 to 26.1% over the past ten years and also a corresponding increase for cobalt, from 4.5 to 10.5%. Of the 26.1% positive to nickel, 5.5% were occupational and 20.5% non-occupational. The increase was assumed to be due to contact with metals or alloys containing nickel, above all with imitation jewellery sometimes worn from a very young age.

In a study population of 1,158 adult volunteers the prevalence of positive patch tests to nickel was 5.8% of which 9% women reacted compared with 0.9% men (Prystowsky *et al*, 1979). There was a strong correlation of nickel allergy with a history of pierced ears, earlobe rash, and jewellery rash. Women appeared to have higher rates of exposure to nickel than men which was reflected in their allergy incidence.

Cobalt: Most comparative studies demonstrate that the incidence of positive patch tests to cobalt has increased in the last twenty years, but not with such a clear effect as nickel (Table 1). In Poland, an increasing positive patch tests to cobalt were found in women, but with the opposite tendency in men (Kiec-Swierczynska, 1990).

Chromium: In contrast to nickel and cobalt the incidence of chromate allergy seems to be decreasing. The North American Contact Dermatitis Group (NACDG) has seen a decline in the prevalence of positive patch tests from 7.6% in 1972 to 2.1% recently (Fowler, 1990). One possible reason for this may be better workplace protective habits which decrease the contact with construction materials and this is supported by data from Finland (Estlander, 1990). Avnstorp (1989) reported the rate of chromate allergy in cement workers has decreased from 10.5% in 1981 to 2.6% in 1987. Likewise, hand eczema prevalence in these workers dropped

from 11.9% to 4.4%. Gollhausen et al (1988) found that the prevalence of positive patch tests to potassium bichromate increased between 1977 and 1983. The higher relative increase in women was explained by the fact that more women now engage in "mens' jobs" (eg. bricklaying) or follow do it yourself trends (Dooms- Goossens, 1980).

Chromate allergy is more common in men, perhaps due to greater exposure to cement and other construction materials. In Spain, the incidence of positive chromate patch tests in women with eczema decreased markedly from 1963 to 1972 (Garcia-Perez et al, 1973). In the period 1963 to 1966 the average incidence of positive patch tests to chromium in women and men with eczema of any type and in any location was high and nearly the same (22% for women, 25.7% for men). In the period 1967 to 1972 the incidence had decreased to 1.6 % for women, but was nearly the same for men (23.3%) (Garcia-Perez et al, 1973). A decrease in the frequency of chromate positive patch tests in women since 1967 was explained by the removal of bichromate from bleaches (Lachapelle et al, 1980).

3.2.2.5. Age Distribution. The age distribution of nickel, cobalt and chromate sensitised persons has been discussed by many, but examined by only a few, investigators. Oleffe et al (1972) patch tested 300 patients and calculated the positive test results in various age groups (0-19, 20-39, 40-59, ≥ 60) and found a different age distribution between nickel, cobalt and chromate reactions and between males and females. The maximum incidence of all three metal reactions, both in males/females, was in the 20-39 age group (43 [43%] for Ni, and 53 [41%] for cobalt and 52 [42%] for chromium) and 40-59 age group (29 [43%] for nickel, and 27 [41%] for cobalt and 39 [42%] for chromium). In males in the 0-19 age group only 14% nickel positives were registered and no cobalt and chromium positives. In the same group 19% females were positive to nickel, 18% to cobalt and 4% to chromium.

Sugai et al (1979) examined the incidence of patch test reactivity to nickel, cobalt and chromium and calculated the test results of 8 groups corresponding to the age decades. For nickel sensitivity, no significant differences were found between the sexes in any decade. For cobalt

it was found that the incidence in the third decade was significantly higher in men than in women. The age and sex distribution of contact sensitivity to chromium tends to be higher in men than in women in the third decade, although the difference was not significant.

In a group of 125 children under the age of 12 years patch tested over a period of 7 years, 60 (48%) had one or more positive reactions. The most common allergens were metals (27.2% = 34). Among these 14.4% (18) reacted to nickel, 5.6% (7) to cobalt, 4.8% (6) to chromate, and 2.4% (3) to other metals (Rademaker and Forsyth, 1989).

A population of 2,653 patients with dermatitis was patch tested in a standard manner over the period of 1977-1988 (Kiec-Swierczynska, 1990). A group of 1,044 patients with at least one positive patch test was investigated further. The incidence of allergy to nickel, cobalt and chromate was statistically calculated and compared in female and male age groups (<30, 30-50, and >50 years). Regarding nickel allergy, the youngest group had the highest incidence in both females and males, but in females the differences were much more marked. Allergy to cobalt showed no clear effect in connection with the age of men, but a decreasing tendency with increasing age in women. Allergy to chromium showed no significant differences between the three age groups in women, but in men an increasing tendency with age was observed.

Test results of 1,312 patients were examined by Husain (1977) and classified according to age in decades. In females the maximum incidence of positive patch test results of nickel, cobalt, chromium and other allergens was in the range of 11-30 years, but in males from 41-50 years. There were few patients in the first and eighth decades.

In the 1950's most patients were sensitised to nickel from suspenders, with the mean age for sensitisation being 30 to 35 years (Calnan, 1956; Wilson, 1956). The mean age for sensitisation has gradually declined in the last decades and today most females develop their contact sensitivity to nickel as teenagers. If significant nickel allergy

resulted from the use of household products then the incidence should become higher with older women, which is not the case (Kaestner, 1988).

Schmiel (1985) examined 503 patients with positive patch tests to nickel who had no current dermatitis and split the results into age groups. The maximum incidence was in the groups 10-19 and 20-29 years. Similar results were reported by Peltonen (1979).

Weber (1986) showed that chromate eczema has the typical profile of an occupational eczema. The highest incidence in males is between 40 and 50 years of age. Chromate positive females have a similar age distribution. Also Young *et al* (1988) found among 83 chromate patch test positive patients (38 male/45 female) 42% were aged between 30 and 50 years, with 33% younger than 30 and 25% older than 50 years.

3.2.3. Human Patch Test Data

Patch testing is the most important tool for diagnosing contact sensitisation to a specific allergen and it is used to investigate the clinical picture of contact dermatitis (cf. Appendix 2). Diagnostic patch tests are also often used to follow up consumer complaints where adverse skin reactions are believed to have resulted from product use.

Test conditions which investigate response to metals when applied to mildly irritated skin, eg. pretreatment of skin with surface active agents, or when metal is injected intradermally, reflect the worst case situations which may occur in everyday life.

3.2.3.1. Dose Response Studies - Nickel. Dose response studies have been conducted on nickel allergic individuals to determine the threshold eliciting concentrations of the metal and the possible enhancement of the skin reaction by solutions of detergent products (Allenby and Goodwin, 1983). Aqueous test solutions of nickel sulphate were applied to the backs of 25 nickel patch test positive volunteers under occlusion for 48 hours. After patch removal, readings were made 1 hour later with further recordings up to 7 days. Aqueous concentrations ranged from

0.012 ppm to 11,200 ppm nickel. Fourteen reacted to 112 ppm nickel and 1 produced a minimal reaction to 11 ppm. These results were broadly confirmed in a smaller panel by Emmett *et al*, 1988. Only one patient reacted to 1 ppm nickel while lower concentrations gave no response. Test samples were also prepared using a 1% aqueous detergent washing powder solution as vehicle. The presence of detergent did not significantly affect the response to nickel under these test conditions.

In a second step, patch test sites were pre-treated for 24 hours by occlusion with water or 0.3% sodium dodecyl sulphate (SDS). Occluded patch tests for 48 hours with 112 ppm nickel (as nickel sulphate) in water or in 1% detergent solution were then performed on the treated sites. Control solutions containing only water or 1% detergent without added nickel were also applied. There was more irritant reaction to both water and 1% detergent solution when these were patch tested on SDS pre-treated sites than on sites pre-treated with water. A significant enhancement of the allergic skin response to nickel was evident at sites pre-treated with water or SDS compared to non-pretreated sites. The reactions observed after SDS pre-treatment were in general more pronounced than those after water pre-treatment.

In a more recent study, twenty nickel allergic volunteers were used to determine the minimum concentration of the metal which would elicit a positive patch test reaction when applied to normal and mildly irritated skin (Basketter and Allenby, 1990). The compromised or mildly irritated skin condition was produced on one arm of each volunteer by twice daily immersions in an 0.5% aqueous SDS solution at 35°C for 10 minutes. This procedure was repeated between 2 and 4 times to produce the required level of skin irritation. Following this pre-treatment, aqueous nickel sulphate solutions were applied under patch to the immersed and non-immersed arms (dorsal aspect) and to the back. The patches were removed after 48 hours. Readings were made at 72 hours and 96 hours. Reactions on the back and normal ie. non-immersed arm were similar: the minimum eliciting concentration of nickel sulphate was 5 ppm. At the lower nickel concentrations of 0.5 and 1 ppm, no reactions were observed on either the back or forearm. By comparison, patch test reactions on

the pre-treated, ie. immersed arm were clearly enhanced. At 5 ppm, 6 of the 20 volunteers reacted and, even at the very lowest concentration of 0.5 ppm nickel, 1-2 of the individuals showed a reaction after pre-treatment with SDS. These data show that after pre-treatment with a surfactant, there is a clear decrease in the minimum eliciting level of nickel sulphate required for a positive patch test response in pre-sensitised individuals.

SITE	NICKEL CONCENTRATIONS			
	10 ppm	5 ppm	1 ppm	0.5 ppm
Back	3	1	0	not done
Normal Forearm	3	3	0	not done
Immersed Forearm	12	6	3	1(2)*

* Reassessment of the results indicates 2 individuals may have reacted to 0.5 ppm (Allenby and Basketter, 1992).

Preliminary results of single open application tests to normal skin in nickel allergic volunteers suggest that the minimal eliciting concentration under these conditions may be as high as 1,000 ppm (Menné, 1991, personal communication).

Allenby and Goodwin (1983) confirmed earlier observations from Kurtin and Orentreich (1954) and Samitz and Pomerantz (1958) that chelation of nickel for example with ethylenediamine tetraacetic acid (EDTA), significantly reduced the ability to elicit an allergic response.

3.2.3.2. Dose Response Studies - Cobalt. In a recent study (Allenby and Basketter, 1989) 9 volunteers who had shown a positive patch test reaction to 1% cobalt chloride in petrolatum participated in a test to establish minimum levels of cobalt required to elicit a positive response under patch. Occluded patches were applied to the back and removed after 48 hours. Test sites were read at 72 hours and 96 hours

post patch application. Concentrations ranged from 0.23 to 2,260 ppm cobalt in either petrolatum or distilled water. Pre-treatment before patch application was by occlusion for 24 hours with dry filter paper discs, with water or with 0.2% aqueous SDS. On normal skin and skin occluded by dry discs, the minimum eliciting concentration of cobalt was 2,260 ppm in the 6 volunteers who reacted. When the skin was pre-treated for 24 hours with water, the minimum eliciting level fell to 226 ppm in one subject. Pre-treatment of the skin with the surfactant for 24 hours resulted in all 6 volunteers reacting to 226 ppm, 5 of the 6 reacting to 23 ppm and 3 reacting to 2.3 ppm. None of the volunteers reacted to 0.23 ppm cobalt.

As in the previous studies with nickel, these data show that, in the presence of a surfactant, there is a clear lowering of the minimum eliciting level of cobalt required for a positive patch test response.

In the same manner as for nickel, EDTA was shown to chelate cobalt and thus substantially to reduce the allergic skin reactions at patch test (Allenby and Basketter, 1989).

3.2.3.3. Dose Response Studies - Chromium. Fourteen volunteers with a positive chromium patch test were patch tested on the back with aqueous solutions of potassium bichromate (hexavalent) and chromic chloride (trivalent) (Allenby and Goodwin, 1983). All patches were removed after 48 hours and the treated skin sites were assessed 1 hour later with further recordings up to 7 days. Concentrations ranged from 0.089 to 1,770 ppm Cr^{6+} and from 88.5 to 17,700 ppm Cr^{3+} . Only two of the fourteen reacted to a solution containing 9 ppm Cr^{6+} and one highly sensitive subject appeared to have a threshold eliciting concentration of 0.6 - 1.2 ppm. For five of the fourteen, 8,850 ppm Cr^{3+} was the threshold eliciting concentration and only the same highly sensitive individual reacted to the lowest level of Cr^{3+} tested (88.5 ppm). At a later retest, this subject reacted to 49 ppm Cr^{3+} but not to 4.4 ppm. As in previous studies (Burrows, 1983), much higher levels (18,850 ppm) of trivalent chromium than hexavalent chromium were normally required to

elicit patch test reactions in chromium allergic volunteers. The chelating agent EDTA had little effect on the reactions.

Using an intradermal test, which the authors regarded as a critical indicator of metal sensitivity, the minimum level of chromium which elicited a response in allergic subjects was 1 ppm (Meneghini and Angelini, 1979).

3.3. DETECTION OF SENSITISATION POTENTIAL IN THE ANIMAL MODEL

It is not appropriate in the context of this report to provide a review of all the studies that have been conducted in animal models with nickel, cobalt and chromium. The information below is only intended to provide a view of their sensitisation potential in the main predictive animal models, the Magnusson and Kligman guinea pig maximisation test (GPMT) and the Buehler test (Botham *et al*, 1991), and to draw attention to important features which may have a bearing on the human risk assessment.

3.3.1. Nickel

A study of the dose response profile to nickel in the GPMT has been reported (Rohold *et al*, 1991). The minimum induction concentration was 60 ppm nickel and the minimum eliciting concentration was 200 ppm nickel. Despite the use of a variety of protocols, nickel salts have proven generally to be of low sensitising potential in animal models (Wahlberg, 1989). Only the Optimisation Test which employs an intradermal challenge gives a very high response rate (Maurer *et al*, 1980). This does not contradict the fact that nickel is a very common contact allergen in man since the nature and extent of human exposure must also be taken into account. Recent studies in the mouse confirm the low capacity to induce T lymphocyte proliferation, which is an index of the primary induction of sensitisation (cf. Appendix 3; Kimber *et al*, 1990).

Whilst nickel was not sensitising in the Buehler test (Buehler, 1965), weakly positive results have been obtained using a fifteen patch induction

protocol (Procter and Gamble, 1991). This study employed five induction patches/week with 25% aqueous nickel sulphate for 3 weeks, followed two weeks later by challenge at 5% in petrolatum.

Chelation of nickel with EDTA can abrogate the response to the challenge in sensitised guinea pigs (Unilever, 1984).

3.3.2. Cobalt

Cobalt salts readily induce sensitisation the guinea pig (Wahlberg and Boman, 1978; Allenby and Basketter, 1989). Allenby and Basketter (1989) reported cobalt chloride to be a strong sensitiser in the GPMT, with a minimum eliciting concentration of 2.3 ppm cobalt. A slight molar excess of EDTA reduced substantially the responses by chelating the cobalt.

No studies of cobalt using the Buehler procedure could be found.

3.3.3. Chromium

Hexavalent chromium has long been recognised as a potent sensitiser in the guinea pig (Magnusson and Kligman, 1970; Goodwin *et al*, 1981). Unpublished data in the GPMT indicates that 0.05 ppm potassium bichromate can sensitise weakly in the guinea pig (Unilever, 1979). Buehler (1965) reported that potassium bichromate sensitised 10% of test guinea pigs.

4. ASSESSMENT OF HUMAN EXPOSURE TO NICKEL, COBALT AND CHROMIUM

4.1. PHYSICO-CHEMICAL PROPERTIES AND ANALYSIS OF NICKEL, COBALT AND CHROMIUM

4.1.1. Physico-Chemical Properties

Nickel: Nickel is present in a number of alloys, eg. stainless steel, non-ferrous alloys (coins, cheap jewellery). There are bivalent and trivalent nickel compounds. Their water solubility varies greatly.

The physico-chemical properties of nickel and the most important nickel compounds are summarised in Table 3.

Cobalt: Cobalt is extensively used as a constituent of many alloys and is an essential nutrient in mammals. As it is also present as an impurity of nickel, the assessment of its toxicological effects may pose some problems. There are bivalent and trivalent cobalt compounds. Their water solubility ranges from insoluble to very soluble.

The physico-chemical properties of cobalt and the most important cobalt compounds are summarised in Table 4.

Chromium: There are tri- and hexavalent chromium compounds. Hexavalent compounds may be soluble or insoluble in water. Chromium compounds are used in many industries, eg. paint, leather and printing. Chromium is used in plating and may also be present in a number of alloys.

The physico-chemical properties of chromium and the most important chromium compounds are summarised in Table 5.

4.1.2. Analysis of nickel, cobalt and chromium

Numerous analytical methods have been developed for the qualitative and quantitative determination of nickel, cobalt and chromium in a wide variety of matrices (US-EPA, 1978; NIOSH, 1984; Sunderman, 1989; IARC, 1990). No specific analytical methods are described for consumer products.

Samples for analysis are evaporated, dried and dry ashed. The residue is fused with hydrochloric, nitric, sulphuric and perchloric acids. Biological samples are directly digested with the above acids. The salts are dissolved and then further analysed. Typical instrumental procedures are:

Atomic Absorption Spectrometry	AAS
Electrothermal Atomic Absorption Spectrometry	EAAS
Inductively Coupled Argon Plasma Emission Spectrometry	ICP
Differential Pulse Anodic Stripping Voltammetry	DPASV
Neutron Activation Analysis	NAA

Details are given in Appendix 4.

"Spot tests" using dimethylglyoxime for nickel, α -nitroso- β -naphthol for cobalt and *sym*-diphenylcarbazide for chromium which may be of help to the diagnostic process have been reviewed (Fregert, 1991).

4.2. TYPES OF CONTACT

4.2.1. Introduction

An intact stratum corneum (SC) is an effective barrier to environmental toxins, general chemicals, microorganisms and mechanical and physical assault (Baker, 1991). The defensive powers of the skin vary greatly between individuals and between different parts of the skin on the same person (Fregert, 1981). Genetic factors and environmental influences determine the resistance of the skin of an individual. This section will concentrate on the types of contact which can influence the penetration of exogenous substances.

4.2.2. Direct Contact with the Metal and their Salts

As described earlier (Section 3) exposure to nickel, cobalt and chromium is common due to daily contact with metal objects or with products contaminated with these metals.

Nickel: Occupational nickel exposure occurs during nickel plating and electroforming of nickel. Other branches of industry which use nickel compounds are battery production, some branches of enamel and glass production, and chemical plants where nickel catalysts are used. Moderate exposure occurs in mechanical engineering and in many industrial plants where nickel alloy is worked up, or where metals are nickel plated. Cement contains nickel but the soluble fraction is low (Angelini and Vena, 1989; Fischer, 1989).

The non-occupational exposure to nickel is generally more important than occupational exposure (Fischer, 1989). Of the 26.1% allergic to nickel in a hospital department in Spain, 5.5% were occupationally related and 20.5% were non-occupational (Romaguera *et al*, 1988). Nickel is found in medicines, fungicides, nickel plated objects, instruments, water taps, coins, scissors, zippers, garter clasps, hair-pins, eyelash curlers, metal frames for eye glasses and costume jewellery. Direct skin contact with nickel is particularly prevalent through the use of jewellery. Costume jewellery made of German silver can contain 10 to 20% of nickel and even jewellery made of white gold can contain up to 15% nickel (Grandjean *et al*, 1989). The use of cheap or expensive jewellery is a special case since exaggerated exposure is promoted through the intimate and occluded contact with the skin. The wearing of wristwatches, tight fitting bracelets, clip-on earrings or earrings for pierced ears are typical examples of intimate skin contact. Ear piercing directly damages the skin and exaggerates the contact even further (Emmett *et al*, 1988; Santucci *et al*, 1989; McDonagh *et al*, 1992).

Because of its special properties, nickel is often found in dental alloys or in patient implants such as joint prostheses, plates and screws for fractured bones, surgical clips, etc (Angelini and Vena, 1989; Fowler, 1990). Nickel is also found in various kitchen utensils eg. cans and tins, pots and pans, electric kettles, nickel plated teaballs, cutlery etc. Water taps, pipes, sinks and bath tubs can all contain and release nickel (Grandjean *et al*, 1989).

Minor amounts of nickel are found in food and drinking water (Veien, 1983; Fischer, 1989). The highest nickel levels are in cocoa and chocolate, soy beans, soy products and other dried legumes, nuts, oatmeal and buckwheat. Seafood may also contain nickel and commercial fats, eg. margarine, may contain traces of nickel due to its use as a catalyst in hydrogenation. The normal total daily intake of nickel through food has been estimated to be between 200 and 600 μg . This amount can increase significantly in vegetarians particularly when chocolate and nuts are included in the diet. Cooking foods, especially those which produce an acidic pH, in stainless steel pots will result in a significant nickel enrichment of the food (Angelini and Vena, 1989).

The nickel levels in drinking water are generally low (Table 7). Except for municipal water supplies coming from large open pit mines, the level of nickel in ground water in several countries is less than 10 ppb. Therefore, except for unusual cases (Lee and Lee, 1990) the direct contribution of drinking water to daily nickel intake is small. On the other hand, drinking water may contain detectable nickel due to leaching from nickel-chromium plated pipes and boilers. Early morning hot water from household taps may contain up to 1.5 ppm nickel. This phenomenon may be attributed to corrosion of the tap or rusting of the lining of the boilers and pipes (Angelini and Vena, 1989; Fischer, 1989).

In addition to the skin, mucous membranes of the mouth, gut and respiratory system may also be exposed to nickel from food and air pollution (Fischer, 1989).

Modern formulations of consumer products, detergents and cosmetics, with the possible exception of mascara, contain only trace levels of nickel (Table 6).

Cobalt: Cobalt is widely distributed naturally in rocks, soils, water and vegetation. It always occurs in nature in association with nickel (Domingo, 1989). Thus, simultaneous exposure to nickel and cobalt is frequent.

Cobalt has been used for the colouring of pottery and glass since pre-Christian times. Today, more than 75% of the world's production of cobalt is used in the manufacture of alloys. Occupational exposure to cobalt in airborne dust mainly occurs in the tungsten and cemented carbide industries. Cobalt compounds are used as dyeing agents in lacquers, varnishes, paints, inks, pigments and enamels. Cobalt is also an important catalyst source for the petroleum industry (Domingo, 1989).

Because nickel and cobalt are present together in most alloys, exposure to nickel, eg. in jewellery, may often result in concomitant sensitisation to cobalt (Menné, 1980; Fischer, 1989). There are reports of ACD due to the cobalt content of metal frames for glasses and in wrist watches (Grimm, 1971).

Cobalt is a vital trace element in animal nutrition. For man, it is an integral and necessary component of vitamin B₁₂. Meats, especially liver and kidney, are major sources of vitamin B₁₂ and thus of cobalt. Fruits, vegetables and cereals contain most of their cobalt in the form of vitamin B₁₂. The average daily intake of cobalt in all forms ranges from 0.3 to 1.77 mg.

Cobalt is not commonly found in drinking water and thus no drinking water limit for cobalt has been set (Domingo, 1989).

Only minor traces of cobalt are found in detergent products and cosmetics (Table 6).

Chromium: Contact with chromium salts can be intimate and exaggerated especially in areas of occupational exposure eg. hand mixing of cement. Such exposure can be avoided by automation of the cement mixing process. Other occupational causes of chromate ACD include primer paints, galvanising, anti-rust agents in coolants, exposure to welding fumes, leather goods, pigments and printing.

Non-occupational exposure to chromium salts occurs through contact with leather products, rubber, stainless steel utensils, chrome alloys and chrome plated objects.

Drinking water limits for chromium have been recommended (Table 9).

Consumer products contain low levels of chromates (Table 6). In former times, potassium bichromate was added as a product component to certain bleaches. These products have since been replaced (Lachapelle *et al*, 1980). In modern formulations, trace chromium is often present in the trivalent form and is thus less bioavailable.

4.2.3. Metal Release

The amount of nickel released from a metal object eg. jewellery, coins etc. depends on the corrosion resistance of the objects and on the contact with sweat, saliva and other body fluids. Due to its chloride content and mildly acidic pH, human sweat may dissolve nickel and leach it from metal objects (Emmett *et al*, 1988). Individuals known as "rusters" with high concentrations of chloride in their sweat are known to have increased potential for causing corrosion of metals (Morgan and Flint, 1989). Gold plated jewellery pieces are often first plated with nickel and then with gold. Prolonged skin contact results in the nickel penetrating the thin gold layer and produces a surface nickel concentration next to the skin which is almost as high as metallic nickel (Fischer, 1989). Even stainless steel objects eg. kitchen utensils can release small amounts of nickel after prolonged contact with sweat or during the cooking of acidic foods (Brun, 1979). Nickel release is particularly important in certain occupations such as hairdressing. Clips, hairpins and some tools are often nickel plated. Repeated contact with solutions used for permanent waves, especially those containing thioglycolic acid, results in soluble complexes being formed with the nickel ions. Under such conditions, nickel plated objects have been reported to release up to 129 µg nickel during the hair treatment (Fischer, 1989). Human sweat may also contain low levels of nickel. Based on a special test with a synthetic sweat solution, Danish authorities have enforced a nickel release limit of 0.5µg/cm²/week for

metal objects which may be worn in prolonged close contact with the skin eg. jewellery, zippers, buttons, spectacle frames etc. (Section 5).

Due to their common co-occurrence, cobalt may be also released from objects concurrently with nickel (Menné, 1980; Fischer, 1989).

ACD due to the release of hexavalent chromium from chromated surfaces has been described (Fregert *et al*, 1970). Chromates are used to cover the protective zinc coating on stainless steel and thus, prevent rapid corrosion or "white rusting" of the steel (Wass and Wahlberg, 1991). Repeated handling of chromated objects (discs, screws etc.) can result in the release of hexavalent chromium due to the action of human sweat. A recent study with chromate sensitive individuals showed that discs releasing $0.6 \mu\text{g}/\text{cm}^2 \text{Cr}^{6+}$ in a 20 minutes period or more elicited a positive response in all panellists. The authors proposed that the mean release of Cr^{6+} from chromated parts should not exceed $0.3 \mu\text{g}/\text{cm}^2$ (Wass and Wahlberg, 1991).

4.2.4. Skin Permeability

The process of sensitisation starts through skin contact with the metal or its salts. The risk of becoming sensitised is increased if the skin is injured. The stratum corneum is covered by a surface film consisting of sebum, sweat and other substances excreted by the skin. The importance of this film lies in its ability to prevent the stratum corneum from drying out. If the film is damaged, eg. by solvents or surface active agents, water is lost from the stratum corneum and cracked, dry skin results (Fregert, 1981). Thus, the penetration of substances causing ACD may be increased.

In contrast to the earlier data from Kvorning and Svendsen (1956), Allenby and Goodwin (1983) showed that the use of a 1% detergent solution as a patch test vehicle did not significantly affect the response to nickel among nickel sensitive individuals. However, pre-treatment of a patch test site with an SDS solution, did produce a significant enhancement of the allergic skin response to cobalt and nickel.

The integrity of the stratum corneum can also be affected by other factors. Mechanical damage will injure the skin, exposure to alkaline materials will destroy the keratin layer and environmental factors such as air humidity will influence skin permeability. If the air humidity is low, which is the case in winter, the skin dries out and cracks. It becomes "chapped". Dry skin is one form of damaged skin and entry of allergic materials is potentiated. On the other hand, too great a skin humidity can increase skin permeability. Metals must be in a soluble state to enter the skin and humid conditions will promote the solubility of the metal through corrosive action. Wet work, eg. in occupations such as hairdressing, impairs the barrier function of the skin. Occlusion such as occurs through the wearing of rubber or plastic gloves, tightly fitting adhesive tapes or jewellery with intimate skin contact (earrings) also enhance skin permeability (Fregert, 1981).

4.3. EXPOSURE LEVELS

The content of nickel, cobalt and chromium found in consumer products is summarised in Table 6. Most publications report measurements for detergents (washing powders or liquids); some present data for dish-washing liquids, surface cleaners, bleaching agents, textile softeners and cosmetics. Hitherto unpublished data on a wider range of consumer products is also presented in Table 6.

The analytical methods used to determine the content of metals in detergents or other consumer products, were in most cases the same (atomic absorption spectrophotometry). Only in older publications was a photometric determination of chromate used (Nater, 1963; Feuerman, 1971; Burrows, 1983). Some authors (Nater, 1963; Feuerman, 1971; Barriere *et al*, 1979; Lachapelle *et al*, 1980; Ebner *et al*, 1978; Nava *et al*, 1987) gave a detailed description of their methods, whereas others (Wells, 1956; Kalveram and Forck, 1977; Wahlberg *et al*, 1977; Kokelj *et al*, 1984; Mueller, 1985; Weiler and Ruessel, 1986; Vilaplana *et al*, 1987; Hostynek and Maibach, 1988) gave only the name or a short description. Details of the analytical procedures used are to be found in Appendix 4.

The concentrations of nickel, cobalt and chromium analysed in consumer products from 15 different European countries and from the USA and Israel are listed in Table 6. The concentrations found do not differ substantially between the countries. Only one significant high concentration (83 ppm) of chromium was found in the Belgian bleach "Eau de Javel". The sodium dichromate, added as a staining agent and a stabiliser, has been removed from "Eau de Javel" since 1976.

The minimum concentrations in consumer products were between 0 and 15 ppm for chromate, between 0 and 10 ppm for nickel and between 0 and 1.1 ppm for cobalt. The maximum concentrations were noted between 0 and 26 ppm for nickel (with one exception of 77 ppm for a hard surface cleaner from the Italian market), between 0 and 5.8 ppm for cobalt and from 0 to 23 ppm (except "Eau de Javel") for chromate. On average, the nickel concentrations were higher than those of cobalt and chromate. The lowest concentrations were obtained for cobalt (Ebner et al, 1978; Mueller, 1985; Nava et al, 1987; Unilever, 1990).

It should be remembered that the results from different sources cannot always be compared directly because not all investigators used the same analytical method. In most cases it can be assumed that the lowest values or values which have the sign "<" (smaller than) in front, are the quantification limits. In some studies a differentiation is made between "detection limits" and "quantification limits". These are detailed below.

Detection limits (ppm)			Quantification limits (ppm)			References
Ni	Co	Cr	Ni	Co	Cr	
-	-	-	10.0	-	-	Wells (1956)
-	-	-	-	-	0.2	Nater (1963)
-	-	-	0.2	-	0.1	Kalveram and Forck (1977)
0.5	0.5	0.3	1.0	1.0	1.0	Wahlberg et al (1977)
0.02	-	-	0.1	-	-	Barriere et al (1979)
-	-	-	-	-	0.03	Lachapelle et al (1980)
-	-	-	-	-	0.1	Kokelj et al (1984)
0.01	0.01	0.01	-	-	-	Lindenmayr (1984)
-	-	-	0.01	0.01	0.01	Mueller (1985)
-	-	-	-	-	0.05	Weiler and Ruessel (1986)
-	-	-	0.1	0.1	-	Vilaplana et al (1987)
0.5 µg/l	-	0.2 µg/l	-	-	-	Nava et al (1987)
-	-	0.1	-	-	0.3	Hostynek and Maibach (1988)
-	-	-	0.5	0.5	0.1	Kaestner (1988)
0.5	0.05	1.0	-	-	-	Procter & Gamble (1990)

5. EXISTING REGULATIONS AND POLICIES

Interest in the exposure of people to nickel, cobalt, chromium and related compounds has been focused in two main areas. Firstly there is the occupational setting where the risk of significant exposure must be controlled. Secondly there is the unintended exposure of consumers through food, drinking water and consumer products. It is interesting to note that the area of major exposure, ie. the wearing of metal objects is at the moment essentially unregulated.

In different countries various policies and regulations have been adopted to control the exposure to nickel, cobalt and chromium. In some countries these policies and regulations have been legally adopted, with exposure limits (workplace and environment) or specified limits (food, drinking water and consumer products); other countries only recommend acceptable levels of nickel, cobalt and chromium.

For nickel, Denmark has regulated the sale of ornamental objects made from alloys containing nickel. The maximum amount of nickel that can be released from these objects is $0.5 \mu\text{g}/\text{cm}^2/\text{week}$ (Menné and Rasmussen, 1990). The EC (1991) is preparing a similar Directive.

The USA regulated the amount of nickel (200 mg/kg), cobalt (200 mg/kg) and chromium (300 mg/kg) in colouring agents for cosmetics (IRPTC, 1987). In EC countries, the marketing of cosmetic products containing chromium is prohibited by a Directive (EEC, 1976).

A synopsis of existing legislations in different countries concerning the presence of these transition metals and related compounds in food, drinking water, consumer products, workplace and the environment is given in Tables 7 - 9.

6. HAZARD/RISK ASSESSMENT

In order to make a hazard/risk assessment for allergic contact dermatitis it is necessary to integrate allergic potential with the mode and extent of human exposure and with the intrinsic sensitivity of the exposed population. Risk, according to an EC definition, is expressed as the probability of the occurrence of an adverse effect.

The trace levels of nickel, cobalt and chromium found in consumer products will not be the primary cause of sensitisation to these transition metals. Exposure levels will be too low and exposure too brief. Schubert *et al* (1987) stated that jewellery, wrist watches and metal clothing buckles are not only the most important cause of primary nickel sensitisation, but also of relapses and persistence of allergy.

The population at risk will be those individuals with an existing allergy to nickel, cobalt or chromium which has resulted from the wearing of jewellery, ear piercing, contact with cement containing chromium etc.. The question must be addressed of the minimum effect levels of the metals to which such individuals might react and compare these to the exposure levels from both normal use and foreseeable misuse of consumer products.

Studies carried out on small populations of nickel and cobalt allergic patients (cf. Section 3.3) have indicated that even when the barrier function of the skin has been impaired substantially by (repeated) surfactant treatment, the lowest metal concentration that may elicit a positive allergic reaction under the conditions of a 48 hour occluded patch will be about 1 ppm. The great majority of allergic individuals will only respond to much higher levels. Although similar studies were not performed for chromium, dose response data on normal skin together with the data of Meneghini and Angelini (1979) suggest that the adoption of about a 1 ppm minimum eliciting concentration would also be a worst case approach.

Levels of nickel, cobalt and chromium in modern consumer products (cf. Section 4.3) are with rare exceptions below 1 ppm. These low levels do not represent a

hazard for the sensitised consumer. Furthermore most consumer products which form the subject of this report are diluted in use, some only a little, eg. hair shampoo, others substantially, eg. dish-washing liquid. For such products, the concentration of transition metal(s) contacting the skin will usually be <0.1 ppm. A further safety margin is provided by the mode of exposure which is open and not occluded as in the patch tests. Also the duration of contact will be for minutes rather than hours. Finally additional safety factors are generated by the presence of chelators and inorganic matrices such as clays which render some of the analysed metal non-bioavailable.

The data of Allenby and Basketter (1989) and Basketter and Allenby (1990) are useful for hazard/risk assessment for the nickel and cobalt allergic consumer using a standard detergent product. Levels in currently available products are less than a few ppm (Table 6). Assuming a level of 5 ppm in the finished product, the actual exposure level would be 0.05 ppm in a washing solution of 1% detergent in water (typically, washing powders are diluted at 0.5 - 1% in water). This level is lower than the minimum eliciting level of nickel and cobalt determined under occlusion on moderately irritated skin of sensitised patients. Furthermore, under normal washing conditions exposure is not occluded and the presence of chelators and clays further reduces the bioavailability of the metal. It should be remembered that 0.05 ppm is the maximum allowable concentration for nickel in drinking water in many countries.

Studies in patients allergic to chromate strongly suggest that at levels of a very few ppm under normal (ie. non-patch test) exposure conditions, the likelihood of eliciting a dermal response in an allergic individual is extremely low. In consumer products chromium is often present in the less sensitising trivalent form and thus, lower levels of the hexavalent form are available for absorption. Finally, dilution factors and mode and length of exposure play a similar role in the consumer hazard assessment as for nickel and cobalt.

In contrast some consumer products are applied undiluted to the skin, perhaps to damaged or eczematous skin, and are left on, eg. skin cream, make-up. Indeed, skin application may be made repeatedly at intervals of a few hours.

Where significant levels of transition metal do occur in such products, problems may be expected, as has occurred with eyeshadow and mascara (Goh et al, 1989; Karlberg et al, 1991). Three patients patch test positive to nickel experienced problems with their "leave on" cosmetic products which was resolved by the use of products with a lower level of nickel (Kasahara and Nakayama, 1990). The nickel level in the suspect cosmetics was 0.1 - 1.0 ppm. Repeated use tests over at least 28 days were required to demonstrate the benefit of "nickel free" replacement cosmetics (Nakayama, 1991, personal communication). However, the paucity of such reports, particularly in view of the frequency of nickel sensitivity in the general female population (up to 10%), supports the argument that the trace levels of transition metals found in consumer products do not represent a significant hazard/risk.

7. CONCLUSIONS AND RECOMMENDATIONS

Despite the improved awareness of the potential for nickel, cobalt and chromium to cause skin allergy, the incidence of sensitisation resulting from contact with them is generally on the increase, especially for nickel. Whilst in general the source of metal contact is well known, in a minority of cases it may not be possible to identify a particular source of contact with the offending metal. Consequently attention has been focused on trace levels of these metals in consumer products as a source of elicited reaction in sensitive people.

The risk of induction and elicitation of an allergic response is related to the concentration of allergen, the area exposed and the length of exposure. Other factors of significance are the mode of exposure of the skin to the allergen, humidity, pH and the presence of other chemical substances.

Dose response studies in allergic individuals demonstrate that the minimum eliciting concentration for nickel, cobalt and chromium in a 48 hours occluded patch test on moderately irritated skin, or by intradermal injection, is about 1 ppm. However, the majority of allergic individuals only react at much higher levels even on moderately irritated skin.

The analytical data in this report demonstrate that consumer products are not an important source of contact with nickel, cobalt or chromium. The allergic subject has many other more significant sources of daily contact such as earrings, jewellery and other metal objects. It is therefore logical and necessary to focus, not on possible trace amounts of metals found in consumer products, but rather on decreasing the high exposure to other sources of these transition metals. The recent Danish legislation and EC draft Council Directive for nickel is a step in this direction. For chromium, close attention to sources of contact in an occupational setting has already paid dividends and a continuation of this should result in a steady decline in the incidence of chromium allergy (Wass and Wahlberg, 1991).

Analytical techniques for precise determination of nickel, cobalt and chromium in a wide range of product matrices require development and validation. It is

recommended that for consumer products, current good practice which ensures nickel, cobalt and chromium contamination is less than 5 ppm of each metal is an acceptable standard. To minimise the risk for very sensitive individuals and when and where standardised analytical techniques permits, it is recommended that the ultimate target should be no more than 1 ppm of each metal in consumer products. Since it is recognised that this target is very unlikely to give rise to ACD, occasional minor deviations above 1 ppm are not seen as posing a significant risk. Even with the strictest controls it is recognised that some allergic individuals may show an elicited reaction.

Finally, it is recommended that further studies of the following topics should serve to enhance the assessments made in this report: research into the relationship between single patch tests and repeated open application of allergen to skin; investigation of the relationship between responses on the back and arm to those on the hands; and lastly, research into how metals penetrate skin and interact with skin components to cause ACD.

TABLE 1
RATIO (PER CENT) OF POSITIVE REACTING PATIENTS TO NICKEL, COBALT AND CHROMATE IN THE PERIOD FROM 1967 UNTIL 1990 AND CHANGE IN PER CENT PER YEAR

Time first last year of examination	sex M/F 2)	Nickel			Cobalt			Chromate			Reference
		first year	last year	change +/- 1)	first year	last year	change +/- 1)	first year	last year	change +/- 1)	
1963/66	M 5)							25.7	23.3	-0.48	
(1965)	F 5)							22.0	1.6	-4.08	Garcia-Perez et al., 1973
1967	M 4)	0.4	0.4	0							
	F 4)	0.9	5.0	+0.51							
1967	M 4)	1.7	4.1	+0.11							Reichenberger et al., 1976
	F 4)	3.9	31.9	+1.33							
1970	M/F 5)	3.0	12.0	+1.80	7.0	15.0	+1.60	10.0	13.0	+0.60	Angelini and Vena, 1989
1970/71	M 4)	6.8	8.6	+0.26	2.7	7.0	+0.61	13.4	9.8	-0.51	Laemmer, 1979
(1971)	F 4)	12.2	21.1	+1.27	5.3	9.1	+0.54	6.6	8.6	+0.29	Schwarz and G-Lueckerath, 1982
1972	M/F 4)	6.9	9.25	+0.59	6.1	5.4	-0.18	10.7	3.6	-1.78	Jarish and Sandor, 1978
1974	M/F 4)	6.7	6.3	-0.08							Lunder, 1988
1972	M/F 4)	11.0	10.7	-0.02				7.6	2.1	-0.31	Fowler, 1990
1972/73	M 4)	6.3	5.5	-0.10				6.3	10.5	+0.52	
	F 4)	13.4	22.7	+1.16				4.2	7.8	+0.45	Lynde et al., 1982
1974	M 4)	3.3	5.6	+0.23	4.1	6.1	+0.20	13.2	6.6	-0.66	
	F 4)	13.3	19.7	+0.64	10.6	8.6	-0.20	12.0	4.8	-0.72	Young and Houwing, 1987
1975	M 5)	2.0	7.1	+0.57	5.6	7.1	+0.17	20.5	8.8	-1.30	
	F 5)	17.8	37.4	+2.18	10.5	10.0	-0.05	3.4	2.1	-0.14	Gailhofer and Ludvan, 1987
1977	M/F 4)				4.5	10.0	+1.10				Vitaplana et al., 1987
1977	M 4)	1.5	3.9	+0.48				4.6	6.5	+0.38	
	F 4)	10.8	16.0	+1.04				2.8	5.8	+0.60	Gollhausen et al., 1988
1977/80	M 5)	4.3	8.5	+0.52	37.1	23.5	-1.70	72.4	51.6	-2.61	
(1978)	F 5)	7.1	43.7	+4.57	20.7	26.8	+0.76	47.9	38.0	-1.24	Kiec-Swierczynska, 1990
1977/83	M 4)	2.6	4.5	+0.27	3.0	3.6	+0.09	5.1	6.9	+0.26	
(1980) 3)	F 4)	13.7	23.9	+1.45	5.9	7.4	+0.21	3.7	4.8	+0.16	Enders et al., 1989
1979	M/F 4)	6.3	9.1	+0.56							Lunder, 1988

1) increase (+), decrease (-) in % per year

2) M = male, F = female

3) for the calculation of change the mean of the time period, given in brackets, is used

Calculation of percentages:

4) patients with positive reactions to Ni, Co or Cr: tested patients

5) patients with positive reactions to Ni, Co or Cr: tested patients with one or more positive patch test reactions

TABLE 2

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TABLE 2 (cont. 1)
INCIDENCE RATE OF NICKEL, COBALT AND CHROMATE CONTACT ALLERGY IN MALES AND FEMALES AND SEX RATIO

Town/Country of examination	Period	Number of tested/pos. patients 2,3)	Nickel			Cobalt			Chromate			Reference
			M %	F %	1) Sex Ratio	M %	F %	1) Sex Ratio	M %	F %	1) Sex Ratio	
Turku/SF	1983-84	1937 2)	2.9	18.0	1 : 6.2							Lammintausta and Kalimo, 1987
Saskatoon/CAN	1983-87	542 2)	8.5	23.1	1 : 2.7				6.1	6.1	1.0 : 1	Hogan et al., 1988
Groningen/NL	1982	141 2)	6.5	26.3	1 : 4.0	8.7		1.1	4.3	7.4	1 : 1.7	Lantinga et al., 1984
Graz/A	1984	1079 3)	7.1	37.4	1 : 5.3	7.1		10.0	8.8	2.1	4.2 : 1	Gailhofer and Ludvan, 1987
Utrecht/NL	1984-86	1785 2)	3.2	20.8	1 : 6.5	4.7		9.3	6.2	3.8	1.6 : 1	Young et al., 1988
7 towns/DK	1985-86	2166 2)	5.1	20.7	1 : 4.1	1.6		6.1	5.0	3.9	1.3 : 1	Christophersen et al., 1989
Barcelona/E	4)	964 2)	29.4	67.8	1 : 2.3	16.2		24.1				Ronaguera et al., 1988
		200 2)	3.0	11.9	1 : 3.6	3.0		3.0				

1) M = males, F = females

For the calculation of percentages as base figures were used:

2) number of tested persons/patients

3) number of tested persons/patients, who had one or more positive patch test reactions

4) the years of examination are not mentioned in the publication

TABLE 3
PHYSICAL PROPERTIES OF NICKEL AND NICKEL COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
METALLIC NICKEL AND NICKEL ALLOYS							
Nickel	7440-02-0	58.69	1455	2730	Lustrous white, hard ferromagnetic metal or powder	Soluble in dilute nitric acid; slightly soluble in hydrochloric and sulphuric acids; insoluble in cold or hot water.	Windholz, 1983
Ferronickel alloy	11133-76-9	--	--	--	Grey solid	Combined properties of metallic iron and nickel, ammonia and alkali hydroxides.	Sunderman, 1984
NICKEL OXIDES AND HYDROXIDES							
Nickel hydroxide	12054-48-7	92.70	230	--	Green crystals or amorphous solid	Nearly insoluble (0.13 g/l) in cold water; soluble in acid, ammonium hydroxide.	Grandjean, 1986
Nickel monoxide	1313-99-1	74.69	1984	--	Grey, black or green powder	Insoluble in water (0.0011 g/l at 20°C); soluble in acid, ammonium hydroxide.	Grandjean, 1986; Sunderman, 1984
NICKEL SULPHIDES							
Nickel disulphide	12035-51-7	122.81	Decomposes at 400	--	Black crystals or powder	Insoluble in water.	Grandjean, 1986; Sunderman, 1984
Nickel sulphide	16812-54-7						
Amorphous -form		90.75	797	--	Black crystals or powder	Nearly insoluble (0.0036 g/l, -form) in water at 18°C; soluble in aqua regia, nitric acid, potassium hydrosulphide; slightly soluble in acids.	Grandjean, 1986; Sunderman, 1984
-form		90.75	--	--	--		
		90.75	--	--	Dark-green crystals		
Nickel subsulphide (-form)	12035-72-2	240.19	790	--	Lustrous pale-yellowish or bronze metallic crystals	Insoluble in cold water; soluble in nitric acid.	Weast, 1986

TABLE 3 (cont. 1)
PHYSICAL PROPERTIES OF NICKEL AND NICKEL COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
NICKEL SALTS							
Nickel acetate	373-02-4	176.78	Decomposes	16.6	Dull green crystals	Soluble in water (166 g/l at 20°C); insoluble in ethanol.	Grandjean, 1986
Nickel acetate tetrahydrate	6018-89-9	248.84	Decomposes	16	Dull green crystals	Soluble in water (160 g/l at 20°C); soluble in dilute ethanol.	Grandjean, 1986
Nickel ammonium sulphate Hexahydrate	25749-08-0	394.94	--	--	--	Soluble in water (104 g/l at 20°C).	Grandjean, 1986
Nickel ammonium sulphate Anhydrous	15699-18-0	286.88	Decomposes	--	Green crystals	Soluble in water (300 g/l at 20°C); less soluble in ammonium sulfate solution; insoluble in ethanol.	Grandjean, 1986; Sax and Lewis, 1987
Nickel carbonate	3333-67-3	118.70	Decomposes	--	Light green crystals	Nearly insoluble (0.093 g/l) in water at 25°C; insoluble in hot water, soluble in acids.	Weast, 1986
Nickel hydroxycarbonate		587.67	Decomposes	--	Light green crystals or brown powder or wet green paste	Insoluble in cold water; decomposes in hot water; soluble in acids.	Sax and Lewis, 1987
Nickel chlorides							
Nickel chloride Anhydrous	7718-54-9	129.60	1001	Sublimes at 973	Yellow deliquescent scales	Soluble in water at 20°C (642 g/l) and at 100°C (876 g/l); soluble in ethanol, ammonium hydroxide; insoluble in nitric acid.	Weast, 1986
Nickel chloride Hexahydrate	7791-20-0	237.70	--	--	Green deliquescent crystals	Soluble in water (2540 g/l at 20°C); very soluble in ethanol.	Grandjean, 1986
Nickel chromate	14721-18-7	174.71	--	--	Black crystals	Insoluble in water.	Weast, 1986

TABLE 3 (cont. 2)
PHYSICAL PROPERTIES OF CHROMIUM AND CHROMIUM COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
Nickel nitrate hexa- hydrate	13478-00-7	290.79	56.7	Decomposes at 136.7	Green deliquescent crystals	Soluble in water (2385 g/l at 0°C), ammonium hydroxide and ethanol.	Weast, 1986
Nickel sulphates Anhydrous	7786-81-4	154.75	Decomposes at 848	--	Pale green to yellow crystals	Soluble in water (293 g/l at 20°C); insoluble in ethanol and diethyl ether.	Grandjean, 1986; Sax and Lewis, 1987
Hexahydrate	10101-97-0	262.84	53.3	--	Blue or emerald green crystals	Soluble in water (625 g/l at 0°C); soluble in ethanol.	Grandjean, 1986; Sax and Lewis, 1987
Heptahydrate	10101-98-1	280.85	99	--	Green crystals	Soluble in water (756 g/l at 20°C); soluble in ethanol.	Grandjean, 1986
OTHER NICKEL COMPOUNDS							
Nickel antimonide	12035-52-8	180.44	1158	Decomposes at 1400	Light copper to mauve crystals	Insoluble in water.	Sunderman, 1984; Grandjean, 1986
Nickel arsenides NiAs	27016-75-7 1303-13-5	133.61	968	--	Grey crystals	Insoluble in hot or cold water, soluble in aqua regia.	Sunderman, 1984
Ni ₁₁ As ₈ Ni ₅ As ₂	12256-33-6 12255-80-0	1244.96 443.39	1000 993	-- --	Platinum grey crystals Grey crystals	Insoluble in water. Insoluble in water.	Grandjean, 1986 Sunderman, 1984; Grandjean, 1986
Nickel carbonyl	13463-39-3	170.73	-25	43	Colourless to yellow liquid	Nearly insoluble (0.18 g/l) in water at 9.8°C; soluble in aqua regia, ethanol, diethyl ether, benzene, nitric acid; insoluble in dilute acids or dilute alkali.	Weast, 1986
Nickelocene	1271-28-9	188.88	171-173	--	Dark green crystals	Soluble in most organic solvents; insoluble in water; decomposes in acetone, ethanol, diethyl ether.	Sax and Lewis, 1987

TABLE 3 (cont. 3)
PHYSICAL PROPERTIES OF NICKEL AND NICKEL COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
Nickel selenide (NiSe)	1314-05-2	137.65	Red heat	--	White or grey crystals	Insoluble in water and hydrochloric acid; soluble in aqua regia, nitric acid.	Weast, 1986
Nickel subselenide (Ni ₃ Se ₂)	12137-13-2	333.99	--	--	Green crystals	Insoluble in water.	Sunderman, 1984; Grandjean, 1986
Nickel telluride	12142-88-0	186.29	Decomposes at 600-900	--	Grey crystals	Insoluble in water; soluble in nitric acid, aqua regia, bromine water.	Sunderman, 1984; Grandjean, 1986
Nickel titanate	12035-39-1	154.57	Decomposes at 1000	--	Yellow crystals	Insoluble in water.	Sunderman, 1984; Grandjean, 1986

TABLE 4
PHYSICAL PROPERTIES OF COBALT AND COBALT COMPOUNDS
(Morrall, 1979; Ferioli et al., 1987)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility in water
Cobalt	7440-48-4	58.94	1495	2870	Silver grey metal	Insoluble
Cobalt (II) oxide	1307-96-6	74.94	1935		Green brown salt	3.13 mg/l
Cobalt (II, III) oxide	1308-06-1	240.8	to CoO 900 - 950		Black salt	Insoluble
Cobalt (III) oxide	1308-04-9	165.86	Decomposes at 895		Black grey powder	Insoluble
Cobalt (III) oxide hydrate		183.88				0.84 mg/l (37°C)
Cobalt (II) chloride	7646-79-9	129.84	Sublimes	1049	Blue crystals	529 g/l (20°C)
Cobalt (II) chloride hexahydrate	7791-13-1	237.93		86 (-6H ₂ O)		767 g/l (0°C)
Cobalt (II) sulphate	10124-43-3	154.99	Decomposes at 735		Red powder	393 g/l (25°C)
Cobalt (II) sulphate heptahydrate	10026-24-1	281.10		96.8 (-7H ₂ O)	Red pink crystals	604 g/l (3°C)
Cobalt (II) nitrate hexahydrate	10026-22-9	291.03		55 - 56 (-3H ₂ O)	Red deliquescent	1338 g/l (0°C)
Cobalt (II) carbonate	513-79-1	118.94	Decomposes		Red crystals	1.1 g/l (15°C)
Cobalt (II) acetate tetrahydrate	71-48-7	249.08		(-4H ₂ O)	Red violet crystals	Soluble
Cobalt (II) naphthenate	61789-51-3					Soluble
Cobalt (II) potassium nitrite	13782-01-9	452.56				9 g/l (17°C)

TABLE 5
PHYSICAL PROPERTIES OF CHROMIUM AND CHROMIUM COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
METALLIC CHROMIUM (0)							
Chromium	7440-47-3	51.996	1900	2642	Steel grey, lustrous metal or powder	Insoluble in water; soluble in dilute hydro- chloric acid and sulphuric acid; insoluble in nitric acid or nitrohydrochloric acid	Windholz, 1983; Weast, 1985
CHROMIUM (III) COMPOUNDS							
Basic chromic sulphate	12336-95-7	165.06	--	--	Green powder	Soluble in water (approx. 700 g/l at 35°C)	British Chrome & Chemical Ltd.
Chromium acetate (hydrate)	1006-30-4 (25013-82-5)	229.14 (247.15)	--	--	Grey green powder (blue violet needles)	Slightly soluble in water; insoluble in ethanol; soluble in cold water, acetone (2 g/l at 15°C) and methanol (45.4 g/l at 15°C).	Windholz, 1983; Weast, 1985
Chromic chloride (hexahydrate)	10025-73-7 (10060-12-5)	158.36 (266.45)	1150 (83)	Sublimes at 1300	Violet crystalline scales	Anhydrous form is insoluble in cold water, slightly soluble in hot water, but insoluble in ethanol, acetone, methanol and diethyl ether. The hydrated form is very soluble in water (585 g/l), soluble in ethanol, slightly soluble in acetone and insoluble in diethyl ether.	Windholz, 1983; Weast, 1985
Chromic nitrate (7.5 hydrate) (nonahydrate)	13548-38-4 () (7789-02-8)	238.03 (373.13) (400.15)	-- (100) (60)	-- Decomposes Decomposes at 100	Pale green powder (brown crystals) (deep violet crystals)	Soluble in water. Both hydrated forms soluble in water; the nonahydrate is soluble in acids, alkali, ethanol and acetone.	Windholz, 1983; Weast, 1985
Chromic oxide	1308-38-9	151.99	2435	4000	Light to dark green, fine crystals	Insoluble in water, acids, alkali and ethanol.	Windholz, 1983; Weast, 1985
Chromic phosphate (dihydrate)	7789-04-0	147 (183.00)	> 1800	--	Violet crystalline solid	Insoluble in water. Hydrated form is slightly soluble in cold water; soluble in most acids and alkali but not in acetic acid.	Windholz, 1983; Weast, 1985

TABLE 5 (cont. 1)
PHYSICAL PROPERTIES OF CHROMIUM AND CHROMIUM COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
Chromic sulphate	10101-53-8	392.16	--	--	Violet or red powder	Insoluble in water; slightly soluble in ethanol; insoluble in acids	Windholz, 1983; Weast, 1985
Potassium chromic sulphate (dodecahydrate)	10141-00-1	283.23 (499.39)	(89)	(400)	(Violet ruby red to black crystals)	Hydrated form is soluble in water (243.9 g/l at 25°C; 500 g/l in hot water); slightly soluble in dilute acids; insoluble in ethanol.	Windholz, 1983; Weast, 1985
CHROMIUM (VI) COMPOUNDS							
Ammonium chromate	7788-98-9	152.07	180	--	Yellow acicular crystals	Soluble in water (405 g/l); insoluble in ethanol, slightly soluble in ammonia, acetone and methanol.	Windholz, 1983; Weast, 1985
Ammonium dichromate	7789-09-5	252.06	170 (dec)	--	Orange red crystals	Soluble in water (308 g/l at 15°C, 890 g/l at 30°C) and ethanol; insoluble in acetone.	Udy, 1956
Barium chromate	10294-40-3	253.33	--	--	Yellow crystals	Very slightly soluble in water (4.4 mg/l at 28°C); soluble in mineral acids.	Windholz, 1983; Weast, 1985
Basic lead chromate	1344-38-3	546.37	--	--	Red crystalline powder	Insoluble in water; soluble in acids and alkali	Windholz, 1983; Weast, 1985
Calcium chromate (dihydrate)	13765-19-0	156.09 (192.10)	(200)	--	Yellow crystalline powder	Slightly soluble in water and ethanol; soluble in acids. Hydrated form is soluble in water (163 g/l at 20°C; 182 g/l at 45°C), acids and ethanol.	Windholz, 1983; Weast, 1985
Chromium trioxide	1333-82-0	99.99	196	Decomposes at 250	Dark red crystals, flakes or granular powder	Soluble in water (625 g/l at 20°C; 674.5 g/l at 100°C), ethanol, diethyl ether and sulphuric and nitric acids.	Udy, 1956

TABLE 5 (cont. 2)
PHYSICAL PROPERTIES OF CHROMIUM AND CHROMIUM COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
Chromyl chloride	14977-61-8	154.9	-96.5	117	Dark red volatile liquid	Decomposes in water and ethanol; soluble in ether, acetic acid, carbon tetrachloride, carbon disulphide, benzene, nitrobenzene, chloroform and phosphorous oxychloride.	Windholz, 1983; Weast, 1985
Lead chromate	7758-97-6	323.18	844	Decomposes	Yellow to orange yellow crystalline powder	Very slightly soluble in water (0.58 mg/l at 25°C); soluble in most acids and alkali but not in acetic acid or ammonia.	Windholz, 1983; Weast, 1985
Nickel chromate	14721-18-7	174.71	--	--	--	Insoluble in water; soluble in nitric acid and hydrogen peroxide.	Windholz, 1983; Weast, 1985
Potassium chromate	7789-00-6	194.20	968.3	Decomposes	Lemon yellow crystals	Soluble in water (629 g/l at 20°C; 792 g/l at 100°C); insoluble in ethanol.	Judy, 1956
Potassium dichromate	7778-50-9	294.19	398	Decomposes at 500	Bright orange red crystals	Soluble in water (49 g/l at 0°C; 1020 g/l at 100°C); insoluble in ethanol.	Windholz, 1983; Weast, 1985
Sodium chromate	7775-11-3	161.97	792	Decomposes	Yellow crystals	Soluble in water (873 g/l at 30°C) and methanol (3.44 g/l at 25°C); slightly soluble in ethanol	Judy, 1956
Sodium dichromate (dihydrate)	10588-01-9 (7789-12-0)	262.00 (298.00)	356.7	Decomposes at 400	Reddish to bright orange crystals	Soluble in water (2380 g/l at 0°C; 5080 g/l at 80°C); and methanol (513.2 g/l at 19.4°C); insoluble in ethanol.	Judy, 1956
Strontium chromate	7789-06-2	203.61	Decomposes	--	Yellow crystalline powder	Slightly soluble in water (1.2 g/l at 15°C; 30 g/l at 100°C); soluble in hydrochloric, nitric and acetic acids and ammonium salts.	Hartford, 1979

TABLE 5 (cont. 3)
PHYSICAL PROPERTIES OF CHROMIUM AND CHROMIUM COMPOUNDS
(after IARC, 1990)

Chemical Name	CAS-Nr	Atomic/ Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Typical Physical Description	Solubility	Reference
Zinc chromate	13530-65-9	181.37	--	--	Lemon yellow crystals	Insoluble in cold water; decomposes in hot water; soluble in acids and liquid ammonia.	Windholz, 1983; Weast, 1985
Zinc chromate hydroxides	15930-94-6	280.74	--	--	Fine yellow powder	Slightly soluble in water; soluble in dilute acids, including acetic acid.	Windholz, 1983; Weast, 1985
OTHER CHROMIUM COMPOUNDS							
Chromium carbonyl	13007-92-6	220.06	Decomposes at 110	Explodes at 210	Colourless crystals or white solid	Insoluble in water; slightly soluble in carbon tetrachloride and iodoform; insoluble in ethanol, diethyl ether and acetic acid.	Windholz, 1983; Weast, 1985
Chromium (II) chloride	10049-05-5	122.9	824	--	White lustrous needles or fused fibrous mass	Soluble in water; insoluble in ethanol and diethyl ether.	Windholz, 1983; Weast, 1985
Chromium dioxide	12018-01-8	83.99	300	--	Brown black crystalline powder	Insoluble in water; soluble in nitric acid.	Windholz, 1983; Weast, 1985

TABLE 6

NICKEL, COBALT AND CHROMIUM CONTENT (ppm) IN HOUSEHOLD PRODUCTS

Type of products	Country	p/l	1)	Number of products	Nickel		Cobalt		Chromium		Reference	
					min.	max.	x + s 2	min.	max.	x + s 2		min.
Detergents (Washing powders/liquids)	A	P		9	1.0	9.5	5.2 + 3.8					
	D	P		4	1.0	2.0	1.7 + 0.5					
	D	17/2		19	0.03	9.5	5) 2.7 + 2.7	<0.01	<0.5	4)		Ebner et al., 1978
	D	10/2		12	0.03	6.3	3.4 + 1.9	<0.01	1.0	0.3 + 0.3		Kaestner, 1988
	D	P		30	1.0	12.0	2.8 6					Mueller, 1985
	D	P		16	1.0	2.0	1.8 + 0.4	0.5	1.0	0.75+0.27		Mueller, 1985
	E	3/1		4	0.1	1.3	0.6 + 0.5	0.1	0.3	0.2 + 0.1		Kalveram and Forck, 1977
	F	P		15	<0.02	4.3	1.36+1.12					Henkel, 1990
	GB	P		6		<10	4,7)					Vilaplana et al., 1987
	I	P		7								Barriere et al., 1979
	I	12/2		14	0.0	18.5	8) 6.3 + 7.1					Wells, 1956
	IL	9)	? 10)	14								Kokelj et al., 1984
	NL	9)	?	21								Nava et al., 1987
	NL	9)	?	11								Feuerman, 1971
	S	9)	?	19	<0.5	5.7			<0.5	3.9		Nater, 1963
	EU	9)	P	71/93 12)								Nater, 1963
	EU	9)	P	17/8	1.0	2.0	7					Wahlberg et al., 1977
	EU	9)	P	16/32	2.0	5.0	7					Burrows, 1983
	EU	9)	P	31/9	5.0	10.0	7					Burrows, 1983
EU	9)	P	18/1	10.0	15.0	7					Burrows, 1983	
EU	13)	P	213	<0.2	16.0	1.0 6					Burrows, 1983	
EU	13)	l	19	<0.15	0.8	0.29 6					Unilever, 1990	
EU	20)	11/1	12	<0.5	2.5	7					Unilever, 1990	
EU	20)	P	3	<0.5	1.5						P. & G. (1985)	
EU	20)	P	2	<1.5	1.5						P. & G. (1988)	
EU	20)	l	1	-	2.5						P. & G. (1989)	
EU	20)	P	6	<1	<2						P. & G. (1990)	

TABLE 6 (cont. 1)
NICKEL, COBALT AND CHROMIUM CONTENT (ppm) IN HOUSEHOLD PRODUCTS

Type of products	Country	p/l	Number of products	Nickel			Cobalt			Chromium			Reference
				min.	max.	x + s 2)	min.	max.	x + s 2)	min.	max.	x + s 2)	
Dish washing liquids	A	l	9	0	5.0	1.2 + 1.6				0.1	3.5	1.0 + 1.3	Ebner et al., 1978
	E	l	3	0.2	1.0	0.7 + 0.5	0	0.16	0.09+0.08				Vilaplana et al., 1987
	I	?	6							0.9	4.7	2.6 + 1.6	Kokelj et al., 1984
	I	5/4	9	0.0	8.5	14) 4.5 + 3.1				0.00	7.8	1.6 + 2.4	Nava et al., 1987
	EU 13)	l	39	<0.2	0.8	0.25 6)	<0.1	0.25	0.24 6)	<0.2	1.4	0.36 6)	Unilever, 1990
Cleaners (Scouring agents, etc.)	D	?	17	0.2	2.4	1.5 6)				0.3	3.5	1.0 6)	Kalveram and Forck, 1977
	D	?	4							0.15	0.58	7)	Weiler and Ruessel, 1986
	E	?	13	0	1.1	0.4 + 0.4	0	0.5	0.2 + 0.2				Vilaplana et al., 1987
	F	l	6	<0.02	0.98	0.2 + 0.4							Barriere et al., 1979
	I	?	5							0.8	3.2	1.7 + 0.9	Kokelj et al., 1984
	I	2/4	6	0.4	10.0	16) 3.1 + 4.7				0.04	10.0	15) 3.6 + 4.2	Nava et al., 1987
	EU 13)	?	8	<0.13	0.3	0.24 6)		<0.25	<0.25 6)	0.4	0.8	0.52 6)	Unilever, 1990
Bleaches	E	l	2	1.2	1.7		1.1	1.4					Vilaplana et al., 1987
	I	l	5	0.03	0.17	0.08+0.05				0.1	0.7	0.4 + 0.3	Nava et al., 1987
	USA	l	7							<0.1	<0.3	4)	Hostynek and Maibach, 1988
	EU 13)	l	2		<0.2	<0.2		<0.25	<0.25	0.6	0.8	0.7	Unilever, 1990
Textile Softener	D	l	5	0.2	0.8	0.4 6)				0.1	0.3	0.2 6)	Kalveram and Forck, 1977
	E	l	1		0			0					Vilaplana et al., 1987
	EU 13)	l	2		<0.2	<0.2		<0.25	<0.25		<0.2	<0.2	Unilever, 1990
Cosmetics 18)	EU 13)	-	42		<1	<1 6)		<1	<1 6)	<1	1.2	<0.1 6)	Unilever, 1990
Shampoos	A		8		<0.01			<0.01			<0.01		Lindenmayr, 1984
Mascaras	EU 13)	-	2	5.6	13.7	9.7	4.5	9.0	6.8	1.0	1.7	1.4	Unilever, 1990

TABLE 6 (cont. 2)
NICKEL, COBALT AND CHROMIUM CONTENT (ppm) IN HOUSEHOLD PRODUCTS

1) p = powders / l = liquids 2) $x + s$ = mean + standard deviation. The outliers were not considered for these calculations. In many publications the single values are not published, therefore the means and standard deviations could not be calculated. When means are given in the publications without single values, these means are shown in this table. 3) additional two outliers of 20 ppm each 4) below the limit of quantification 5) additional one outlier of 22.5 ppm 6) standard deviation cannot be calculated because single values are not mentioned but means are given in the publication 7) as 6) but means are not given in the publication 8) additional three outliers of 22.8, 22.8 and 25.7 ppm 9) Detergents (washing and dishwashing agents, cleaners, bleaches) no differentiation was possible? = 10) The number of powdered/liquid products are not mentioned in the original publications 11) additional one outlier of 23.2 ppm 12) first number refers to nickel, the second one to chromium 13) product samples taken from 15 European countries 14) additional one outlier of 21.4 ppm 15) additional one outlier of 20 ppm, but in a second analysis of the same product 0.23 ppm were found 16) additional two outliers of 25.7 and 77.1 ppm, but in a second analysis of the same products 14.2 and 0.21 ppm resp. were found 17) below the detection limit 18) Cosmetics: 4 toothpastes, 11 (hand) creams, 6 shampoos, 3 conditioners, 1 hair dye, 4 roll on deos, 3 stick deos, 6 aerosol deos, 1 facial wash, 1 liquid soap, 1 nail varnish, 1 lipstick 19) additional one outlier for chromium between 15 and 20 ppm. 20) product samples taken from various European countries.

COMMENT TO TABLE 6

The concentrations of nickel, cobalt and chromium analysed in consumer products from 15 different European countries and the USA are listed in Table 6. The concentrations found do not differ substantially between the countries. Only one significant high concentration (83 ppm) of chromate was found in the Belgian bleaching agent "Eau de Javel" (Lachapelle *et al*, 1980).

The mean concentrations in consumer products were between <0.1 and 6.8 ppm for chromate, between <0.1 and 9.7 ppm for nickel and between <0.1 and 1.4 for cobalt. The minimum concentrations found were between 0 and 15 ppm for chromate, 0 and 10 ppm for nickel and 0 and 1.1 ppm for cobalt. The maximum concentrations were noted from <0.1 to 20 ppm for chromate, but some outliers were found with higher values (23 ppm for a detergent, Feuermann, 1971) and for bleaches, especially from the Spain, Italian, French and Belgian market 15 years ago and earlier (Dooms-Goossens *et al*, 1980; Lachapelle *et al*, 1980). The maximum concentrations for nickel were between 0 and 18.5 ppm, but 6 outliers were found in the reviewed publications, 5 between 21 and 26 ppm and one with 77 ppm (Nava *et al*, 1987). The high values found by Nava *et al* (1987) could not be reproduced. A second analysis gave significantly lower values (see footnotes Table 6). The maximum concentrations of cobalt were between 0 and 5.8 ppm. Although only few values are available, cosmetics have very low values of chromium, nickel and cobalt independently of the kind of cosmetic and the European country. Mascaras may be an exception with two samples having higher values.

On average, the nickel concentrations were higher than the concentrations of chromate and cobalt, but the lowest concentrations were registered for cobalt (Ebner *et al*, 1978; Mueller, 1985; Nava *et al*, 1987).

It should be remembered that results from different sources cannot always be compared directly because not all investigators used the same method. In most cases it can be assumed that the lowest written values or values which have the sign "<" (smaller than) in front of it, are the detection limits. Such figures (mg/kg or ppm) were found in the following publications: 1.0, 0.5 and 0.5 for

chromium, nickel and cobalt respectively (Kaestner, 1988); 0.01 for nickel, cobalt and chromium each (Mueller, 1985); 0.1 and 0.2 for chromium and nickel (Kalveram and Forck, 1977); 0.1 for nickel and cobalt both (Vilaplana *et al*, 1987); 0.1 for nickel, but the detection limit is mentioned as 0.02 ppm (Barriere *et al*, 1979); 10 for nickel (Wells, 1956); 0.1 for chromate, but in the publication 0.1 $\mu\text{g/l}$ is mentioned (Kokelj *et al*, 1984); 0.01 for chromium and nickel both, but in the publication the analytical sensitivity is given with 0.2 $\mu\text{g/l}$ for chromium and 0.5 $\mu\text{g/l}$ for nickel (Nava *et al*, 1987); 0.2 for chromium (Nater, 1963); 1.0 for chromium, nickel and cobalt (Wahlberg *et al*, 1977); and 0.3 as limit of quantification for chromium and 0.1 as limit for detection of chromium (Hostynek and Maibach, 1988).

Table 7 - NICKEL: EXISTING REGULATIONS AND POLICIES (IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Belgium		X			AIR: TWA 1 mg/m ³ for metallic Ni; 0.1 mg/m ³ for Ni compounds as Ni.	
Belgium (1)		X			AIR: TWA Ni oxides and sulphides: 1 mg/m ³ ; Ni carbonyl: 0.7 mg/m ³	
Council for Mutual Economic Assistance (CMEA)		X	Max. Permiss. Conc. recommended: milk products: 0.1 mg/kg meat products: 0.5 mg/kg fish products: 0.5 mg/kg cereals: 3 mg/kg vegetables: 0.5 mg/kg fruits: 0.5 mg/kg other prod.: 0.2-8 mg/kg beverages: 0.3 mg/kg (applies to Ni and its compounds as Ni).			
Denmark (2)	X			The sale of the following metal objects made from Ni containing alloys or with Ni containing surface coating is banned, if Ni release exceeds 0.5 ug/cm ² /week: ear ornaments and and ear stickers; necklaces, bracelets and chains, finger rings, hair clips; wrist watch backs cases, watch straps and tighteners; spectacle frames; garments equipped with buttons, tighteners, rivets, zippers and metal marks which will by normal use come into close contact with the skin		
EEC (3)	X		Drinking water: Max. Acc. Conc.: 50 ug/l			

Table 7 (cont. 1)
NICKEL: EXISTING REGULATIONS AND POLICIES (IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Canada		X			AIR: Max. Permiss. Conc. TWA 1 mg/m ³ for metallic Ni; TWA 0.1 mg/m ³ for Ni compounds as Ni.	
Canada (1)		X			AIR: TWA 1 mg/m ³ (insol. water oxides and sulphides); 0.007 mg/m ³ (Ni carbonyl).	
France (1)		X			AIR: TWA 1 mg/m ³ (metal - as dust)	
Germany (4)	X		WATER: Maximum permissible concentration 50 ug/l		AIR: TRK 0.5 mg/m ³ (as Ni in total dust), as Ni metal, sulphide, oxide and carbonate. TRK: 0.05 mg/m ³ as Ni compounds in respirable particles. TRK: 0.7 mg/m ³ as Ni tetracarbonyl	
Italy (1)	X		WATER: Maximum permissible concentration 50 ug/l			
Italy (4)		X			AIR: TWA 1 mg/m ³ (water insol. comp.); 0.1 mg/m ³ (water sol. comp.); 0.07 mg/m ³ (Ni carbonyl).	

Table 7 (cont. 2)
NICKEL: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Japan		X			AIR: Max. Accept. Conc. TWA 1 mg/m ³	
Japan (1)		X			AIR: TWA 1 mg/m ³ (water insol. comp.); 0.07 mg/m ³ (Ni carbonyl).	
Netherlands (1)		X			AIR: TWA 1 mg/m ³ (water insol. oxides and sulphides); 0.007 mg/m ³ (Nickel carbonyl).	
Norway (1)		X			AIR: TWA 0.4 mg/m ³ (water insol. comp.); 0.4 mg/m ³ (water sol. comp.).	
Soviet Union	X					SURFACE WATERS FOR FISHING: Max. Accept. Conc.: 0.01 mg/l (applies to Ni and its compounds as Ni).
Soviet Union	X				AIR: Max. Accept. Conc. CLV 0.005 mg/m ³ (Aerosol) (applies to Ni salts in form of hydroaerosols, as Ni).	
Soviet Union					AIR: Max. Accept. Conc. 0.002 mg/m ³ ; as Ni (applies to water solutions Ni salts). 0.001 mg/m ³ (applies to metallic Ni).	
Soviet Union	X					WATER SURFACE: Max. Accept. Conc. 0.1 mg/l (applies to Ni and its inorganic compounds as Ni).

Table 7 (cont. 3)
NICKEL: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Soviet Union	X				AIR: Max. Accept. Conc. CLV 0.05 mg/m ³ (aerosol) (applies to metallic Ni, its oxide, sulphide and mixture of these compounds).	
Soviet Union	X		Max. Permiss. Conc.: fish products: 0.5 mg/kg meat products: 0.5 mg/kg milk products: 0.1 mg/kg cereals: 0.5 mg/kg vegetables: 0.5 mg/kg fruits: 0.5 mg/kg beverages: 0.3 mg/kg (applies to Ni and its compounds as Ni).			
Soviet Union	X					SOIL: Max. Accept. Conc.: 4 mg/kg (applies to mobile forms of Ni tractable by ammonium acetate sulphur solution pH = 4.6).
Soviet Union(1)	X				AIR: TWA 0.05 mg/m ³ (water insol. comp.); 0.005 mg/m ³ (water sol. comp.); 0.0005 mg/m ³ (Ni carbonyl).	
Sweden	X				AIR: 1d TWA 0.5 mg/m ³ of metallic Ni; 1d TWA 0.1 mg/m ³ of soluble Ni compounds, Ni oxide, Ni carbonate, as Ni.	

Table 7 (cont. 4)
NICKEL: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Not Bin- Leg. ding Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Sweden (1)	X			AIR: TWA 0.01 mg/m ³ (water insol. comp.); 0.007 mg/m ³ (Ni carbonyl).	
Switzerland	X			AIR: MAK TWA 0.5 mg/m ³ for dust of Ni metal (except alloys), sulphide oxide and carbonate, as Ni; TWA 0.05 mg/m ³ for dust of water soluble Ni compounds (as Ni).	
Switzerland (1)	X			AIR: TWA 1 mg/m ³ (water insol. oxides and sulphides); 0.007 mg/m ³ (Ni carbonyl).	
United Kingdom	X			AIR: 8 h-TWA 1 mg/m ³ for element. Ni; 8 h-TWA 0.1 mg/m ³ for soluble Ni comp.; STEL 10 min-TWA 0.3 mg/m ³ ; 8 h-TWA 1 mg/m ³ for insoluble Ni compounds as Ni, STEL 10 min-TWA 3 mg/m ³ .	
United Kingdom (1)	X			AIR: TWA 0.5 mg/m ³ (water insol. comp.); 0.1 mg/m ³ (water sol. comp.); 0.13 mg/m ³ (Ni carbonyl).	
U.S.A.	X	FOOD AND BEVERAGES: Max. Permiss. Conc.: The food additive trifluoromethane sulphonic acid must contain no more than 30 mg/kg of Ni or other heavy metal.			

Table 7 (cont. 5)
NICKEL: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
U.S.A.	X		Max. Permiss. Conc. in specified straight colours used in food: traces 0.003% (0.03 g/kg).	COSMETIC COLOURING AGENTS: 200 mg/kg DRUG COLOURING AGENTS: 200 mg/kg		
U.S.A.	X				AIR: TWA 1 mg/m ³ of metallic Ni and soluble Ni compounds as Ni.	
U.S.A.	X				AIR: TLV-TWA 1 mg/m ³ of metallic Ni; 0.1 mg/m ³ of soluble compounds of Ni.	
U.S.A.	X				AIR: TWA mg/m ³ (under revision) (water insol. comp.); 0.1 mg/m ³ (under revision) (water sol. comp.); 0.007 mg/m ³ (under revision) (Ni carbonyl).	

TLV: threshold limit value

TWA: time weighted average for 8 hours

CLU: ceiling limit value

MAC: Maximale Arbeidsconcentratie (NL)

STEL: short term exposure limits

TRK: Technische Richtkonzentration (D)

(1) ECETOC - Technical Report 33

(2) Denmark - Statutory Order No. 472, June 27, 1989

(3) EEC Act January 1983

(4) Maximale Arbeitsplatzkonzentration und Biologische Arbeitsstofftoleranzwerte, 1991.

Table 8
COBALT: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Belgium		x			AIR : TLV*-TWA: 0.05 mg/m ³ STEL: 0.1 mg/m ³ (applies to metal and fumes expressed as Co)	
Finland		x			AIR: Max.Perm.Conc.: TWA 0.1 mg/m ³ (applies to Co and its compounds as Co).	
Germany (4)	x				AIR: TRK 0.5 mg/m ³ (as Co in total dust), as Co metal, Co oxide and Cobaltsulphide (production of Co powder and catalysts; hard metal and magnet production, pressing and processing of unsintered articles)	
Italy		x			AIR: TLV 0.1 mg/m ³ . Provisional for fumes and dust.	
The Netherlands		x			AIR: Max. Limit TWA: 0.1 mg/m ³ of dusts and smoke as Co.	

Table 8 (cont. 1)
COBALT: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Not Bin- Leg. ding Bin-		Food Drinking Waters	Consumer Products	Workplace	Environment
	ding	ding				
Soviet Union	x			AIR: Max. Accept. Conc. 0.001 mg/m ³ (applies to metallic Co).		
Soviet Union	x					WATER SURFACE: Max. Accept. Conc. 0.1 mg/l (applies to Co and its inorganic compounds as Co).
Soviet Union	x					SURFACE WATER FOR FISHING: Max. Accept. Conc. 0.01 mg/l. SEAWATER 0.005 mg/l (applies to Co inorganic compounds as Co).
Soviet Union	x			AIR: Max. Accept. Conc. CLV* (0.5 mg/m ³ (aerosol)).		

Table 8 (cont. 2)
COBALT: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
U.S.A.	x		Cobaltous salts (chloride acetate and sulphate) and their derivatives are prohibited from use in human food. Food containing added or detectable level is adulterated.			
U.S.A.	x		Max. Permiss. Conc. Specified drug colouring agents 200 mg/kg. Specified cosmetic colouring agents 200 mg/kg.			
U.S.A.	x				AIR: Perm. Exp. Limit TWA 0.1 mg/m ³ of Cobalt fumes and dust.	
U.S.A.		x			AIR: TLV=TWA 0.05 mg/m ³ of Cobalt dust and fumes as Co.	
U.S.A.	x				AIR: Co metal, dust and fume: TWA 0.05 mg/m ³ as Co. Cobalt carbonyl and Cobalt hydrocarbonyl: TWA 0.1 mg/m ³ as Co.	

TABLE 9
CHROMIUM: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Belgium	X				AIR: TWA 0.5 mg/m ³ (Cr, Cr(2) and Cr(3) compounds, as Cr. TWA 0.05 mg/m ³ (Cr(6) water soluble and insol. compounds chromites and chromates, as Cr).	
Council for Mutual Economic Assistance (CHEA)	X		Max. Permiss. Conc.: milk products: 0.1 mg/kg meat products: 0.2-0.5mg/kg fish products: 0.3 mg/kg cereals: 0.4 mg/kg vegetables: 0.2 mg/kg baby foods: 0.1 mg/kg other food prod.: 0.5 mg/kg beverages: 0.05 mg/kg (applies to Cr and its compounds as Cr).			
E.E.C.	X			The marketing of cosmetic products containing Cr is prohibited (EEC Dir. 76/768).		
E.E.C.		X	DRINKING WATER: < 50 ug/Cr/l			
E.E.C.	X		< 100 mg/kg Cr may be obtained in colouring matters authorised for use in foodstuffs intended for human consumption. (Directive 23/10/62).			

TABLE 9 (cont. 1)
CHROMIUM: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Binding	Not Leg. Binding	Food Drinking Waters	Consumer Products	Workplace	Environment
Germany (1)	X		DRINKING WATER: Maximum permissible concentration 50 ug/l		AIR: TRK* (Cr6+ compounds in form of dusts/aerosols) 0.2 mg/m ³ (are welding) 0.1 mg/m ³ (others)	
Finland		X			AIR: Max. Permiss. Conc. TWA 0.5 mg/m ³ of metallic Cr; 0.5 mg/m ³ for Cr(2) and Cr(3) compounds, as Cr; 0.05 mg/m ³ for Cr(6) compounds as Cr.	
Italy		X			AIR: TLV 0.5 mg/m ³ (insoluble compounds, as Cr); 0.05 mg/m ³ (chromic acid and chromates as Cr)	
Italy (2)	X		DRINKING WATER: Maximum permissible conc. 50 ug/l			
Japan	X					WATER: Emissions (discharges) Max. Permiss. Conc. Effluent standard: 2 mg/l.

TABLE 9 (cont. 2)
CHROMIUM: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
Iran		X			AIR: Max. Accept. Conc. TWA: 0.5 mg/m ³ (tentative value. Applies to metallic Cr and its alloys).	
Netherlands		X			AIR: TWA 0.5 mg/m ³ (Cr and sol. comp., as Cr); TWA: 0.05mg/m ³ (chromic acid and chromates as Cr); TWA: 0.05 mg/m ³ (water insoluble chromate salts).	
Switzerland						
United Kingdom						
United States						
West Germany						
France						
Sweden						
Denmark						
Finland						
Belgium						
Italy						
Spain						
Portugal						
Greece						
Turkey						
Japan						
South Korea						
China						
India						
Pakistan						
Bangladesh						
Sri Lanka						
Malaysia						
Singapore						
Thailand						
Philippines						
Indonesia						
Brunei						
Mexico						
Central America						
Caribbean						
South America						
Europe						
Asia						
Africa						
Oceania						
Other						

TABLE 9 (cont. 3)
CHROMIUM: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Not Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
United Kingdom	X	Shall be given satisfactory evidence to show that a natural mineral water extracted for human consumption contains no toxic substances such as Cr in an amount exceeding 50 ug/l.			
United Kingdom	X			AIR: Cr: TWA 0.5 mg/m ³ ; for Cr(2) comp.: 8h-TWA: 0.5 mg/m ³ as Cr; for Cr(6) compounds 8-h TWA 0.05 mg/m ³ as Cr.	
U.S.A.	X	DRINKING WATER: Water delivered to the free flowing outlet of the ultimate user may not be permitted to contain more than 0.05 mg/l of Cr.			
U.S.A. (3)	X	Colour additives used in food, drugs and cosmetics: < 50 mg/kg.			
U.S.A.	X	Bottled water not more than 0.05 mg/l of Cr.			
U.S.A.	X	Specified drug colouring agents 0.75-1 g/kg as Cr O in 2% NaOH extract.			

TABLE 9 (cont. 4)
CHROMIUM: EXISTING REGULATIONS AND POLICIES
(IRPTC, 1987)

Country	Leg. Bin- ding	Not Leg. Bin- ding	Food Drinking Waters	Consumer Products	Workplace	Environment
U.S.A.	X		Certain specified straight colours used in food, drugs and/or cosmetics: trace - (30 mg/kg)	Certain specified straight colours used in food, drugs and/or cosmetics: trace - 0.003% (30 mg/kg).		
U.S.A.	X				AIR: TLV 0.05mg/m ³ (Cr and insol. comp. as Cr); 0.05mg/m ³ (Chromic acid and chromates as Cr).	
U.S.A.	X				AIR: TWA 0.5mg/m ³ as metallic Cr, Cr(2) comp. as Cr, Cr(3) comp. as Cr; 0.05 mg/m ³ water sol. Cr(6) comp. as Cr, water insol. Cr(6) comp. as Cr; chromite ore processing, as Cr.	
U.S.A. (4)	X				AIR: Chromium (2) and Chromium (3) compounds, as Cr, TWA 0.5 mg/m ³ Cr metal, as Cr TWA 1 mg/m ³ .	
W.H.O.	X		DRINKING WATER: Guideline Level: 0.05 mg/l			

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APPENDICES

APPENDIX 1

1. GLOSSARY OF TERMS

Adjuvant: a substance used to enhance the immune response in a non-specific manner, such as Freund's Complete Adjuvant.

Allergic contact dermatitis (ACD): a cell mediated immunological response to chemicals with a molecular weight generally less than 1,000 that contact and penetrate the skin.

Allergy: a clinical manifestation of hypersensitivity. Allergy is defined classically as an antigen specific altered reactivity of the host to antigen.

Antigen: foreign material which can induce an immune response (see Hapten).

Antigen presenting cells: a number of cell types which concentrate, process and present antigens to lymphocytes in order to induce an immune response.

Challenge: treatment designed to elicit a skin reaction in a sensitised animal/man.

Dermal irritation: the production of reversible non-immune inflammatory changes in the skin following the application of a substance.

Erythema: redness of the skin produced by vascular congestion or increased perfusion.

Hapten: a small molecule, which although foreign, cannot be recognised by the immune system unless combined with a suitable carrier protein.

Hazard assessment: involves the integration of the potential of a chemical to harm man or the environment and the potential for exposure to a chemical.

Hazard identification: the evaluation of the hazardous properties inherent in a substance.

Hypersensitivity: an adaptive immune response against an antigen which occurs in an exaggerated or inappropriate form and which can lead to tissue damage (see allergy).

Langerhans cells: the antigen presenting cell of (human) skin.

Lymphokine: generic term for a number of molecules (excluding antibody) produced by lymphocytes and involved in mediating cellular interactions during an immune response.

Memory cells: circulating antigen specific T lymphocytes which arise by clonal expansion following sensitisation.

Oedema: the presence of abnormally large amounts of fluid in the intercellular tissue spaces.

Risk assessment: As a risk is usually expressed as the probability of the occurrence of an adverse effect, the term risk assessment should only be used when probabilities are calculated that a hazard will occur under specific exposure conditions. The term is often confused with hazard assessment and is frequently misused as a comprehensive term to cover any evaluation of substances.

Sensitisation: the development of an expanded population of T lymphocytes for a specific antigen which can give rise to a delayed allergic response upon challenge with that antigen.

Stratum corneum: the horny outer layer of the skin.

T Lymphocytes (T cells): cells of bone marrow origin which mature in the thymus and then migrate into blood, lymph and lymphoid tissue. They express antigen receptors and are divided functionally into helper, suppressor and cytotoxic subpopulations.

APPENDIX 2

METHODOLOGY TO IDENTIFY CONTACT ALLERGENS IN MAN (PATCH TEST)

The process of sensitisation leads to an antigen specific hypersensitivity of the skin. This can be demonstrated by application of the causative substance to a normal skin site, which is usually done under occlusion (Appendix 3).

A small amount of hapten applied under occlusion to a small area of the skin, via a patch, is able to stimulate the "secondary response" and cause a delayed erythematovesicular reaction. This response is morphologically and histologically identical to a spontaneous allergic eczematous lesions. For these reasons the patch test is a miniature and unique direct in vivo test.

Properly applied and correctly interpreted, patch test reactions are, at present, acceptable as "scientific proof of the cause of dermatitis and may be medicolegally important" (Fisher, 1986).

1. THE TECHNIQUE OF PATCH TESTING

The suspected allergen, suitably diluted, is placed in a chamber of which the commonest example is the Finn Chamber (Pirilae, 1975). This is an inflexible aluminum concave disc, 8 or 12 mm diameter and 0.5 mm deep, where the suspected allergen is placed. The raised border of the chamber creates a tight occlusion of the test materials. These chambers are normally held in place with a hypoallergenic tape such as a Scanpor.

Generally patch tests are performed on the skin of the back and are left in place for 48 hours. After removal, the test sites are marked. Opinions concerning the optimal time for reading differ. Generally this is performed 72 or 96 hours after the initial application of the patch, although periods up to 7 days have been recommended in order to optimise the detection rate for some specific allergens (MacFarlane et al, 1989; Fowler, 1990).

2. TEST CONCENTRATION AND VEHICLE TO BE USED FOR PATCH TESTING

Materials for patch testing should be diluted to the maximum concentration which does not provoke reactions in non sensitised persons. The choice of a correct concentration is often difficult. Too high a concentration is potentially irritating, whilst too low a concentration evokes no response, except in strongly sensitised patients. In this situation, patch tests on a sufficiently large group of control persons are still the best method to select an adequate test concentration.

The vehicle used should not be sensitising or irritating. Petrolatum is the vehicle most frequently used. Generally speaking, the most stable and the least volatile vehicle is the best.

3. INTERPRETATION OF PATCH TEST RESULTS

There are two problems encountered when interpreting patch test results. Even when an optimal patch test concentration has been selected, it may prove very difficult to distinguish weak irritant from weak allergic reactions. An irritant reaction is recognised by the following characteristics: it is strictly confined to the area to which the test has been applied; it may appear as erythema, oedema occasionally with bullous signs and it is usually a rapidly regressing reaction. A false negative result may arise when for example the test concentration is not sufficient to elicit a response even though the subject is indeed sensitised or when a substance is applied in an unsuitable vehicle. Interpretation requires adequate experience under supervision of trained personnel. For further details the reader is referred to the literature (Fischer and Maibach, 1991).

4. COMPLICATIONS

Patch testing may be considered a fairly innocuous method of investigation. Only occasionally is the patient exposed to the hazard of iatrogenic sensitisation or an excessive degree of skin reaction. Further in such cases sensitisation is detected by the appearance of an erythematous and vesicular reaction at the site where the substance was applied, a week or two after the patch testing ("flare up"). A positive reaction, particularly if pronounced, may reactivate existing dermatitis or cause new lesions.

Contact urticarial reactions may be observed occasionally (Maucher, 1983).

5. CLASSIFICATION OF PATCH TEST REACTIONS

The International Contact Dermatitis Research Group (Fregert, 1981) has recommended a scoring system. The interpretation key is:

- +? = doubtful reaction, faint erythema only;
- + = weak positive reaction, eg. erythema, infiltration, possibly papules;
- ++ = strong positive reaction, erythema, infiltration, papules, vesicles;
- +++ = extreme positive reaction, intense erythema and infiltration and coalescing vesicles;
- = negative reaction;
- IR = irritant reaction of different types;
- NT = not tested.

Further details and reviews of patch test techniques may be found in Sertoli and Fabbri (1974), Malten et al (1976), Meneghini (1983) and Hjorth (1991).

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APPENDIX 3

MECHANISM OF ALLERGIC CONTACT DERMATITIS

ACD is a cell mediated immunological response to chemicals with a molecular weight generally less than 1,000 that contact and penetrate the skin. Interaction of the chemical (or hapten if it requires linkage to a "carrier" protein for recognition) with the skin associated lymphoid tissue results in the activation, proliferation and dissemination of antigen specific T lymphocytes (or T cells). This is the first step, called the induction phase, in the sequence of events leading to skin sensitisation. The induction phase therefore requires contact with the foreign chemical and penetration through the natural skin barrier, hence the requirement for relatively small molecular size. Having crossed the barrier, the chemical may first be changed within the skin before forming a reactive hapten eg. some simple chemicals require the action of light before they can "react". The Langerhans cells (LC), which comprise about 2% of the epidermis in man, take up the chemical in the skin and transport it to the draining lymph nodes.

The foreign chemical becomes associated with an LC transmembrane glycoprotein called the Class II histocompatibility antigen. This is an important event because T cells only recognise the chemical when it is associated with Class II determinants. Lymph node T cells with complementary receptors specific for the chemical or antigen recognise the antigen-Class II complex. Recognition is followed by rapid proliferation of the T cells and the subsequent differentiation and dissemination of effector and memory T cells. These cells circulate throughout the body via the blood and lymphatic systems and retain their specificity for the original chemical. The individual is now sensitised.

In the second phase of skin sensitisation, a subsequent cutaneous contact with the original or a cross reactive chemical may result in the characteristic inflammatory skin reaction. The circulating memory T cells recognise the antigen formed at the application site and undergo rapid activation, secreting lymphokines which exert a variety of effects on other inflammatory cells, including fluid accumulation, swelling of blood vessels, lymphocyte infiltration and local tissue destruction at the contact site. Thus, after elicitation, the skin of the sensitised individual is characterised by erythema, oedema, vesiculation and pruritus.

Although not life threatening, ACD can be very debilitating. Because of the memory T cells, the condition is persistent. Once sensitised to a chemical, an individual is at risk of dermatitis whenever exposed to eliciting levels of the same or a cross reactive chemical.

For further details details of recent advances in the immunology of ACD see von Blomberg et al (1991).

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APPENDIX 4

ANALYSIS OF NICKEL, COBALT AND CHROMIUM

1. GENERAL PROCEDURES

1.1. NICKEL

Atomic absorption spectrometry (AAS), electrothermal atomic absorption spectrometry (EASS), differential pulse anodic stripping voltametry (DPASV) or inductively coupled argon plasma emission spectrometry (ICP) are the most common methods for analysis of nickel (NIOSH, 1984; Kettrup *et al*, 1985). EAAS (Sunderman *et al*, 1984) and DPASV (Stoeppler, 1981; Ostapczuk *et al*, 1983; Uto *et al*, 1985) are currently the most practical and reliable instrumental techniques to measure nickel. The detection limits for by EAAS ranges from 10 ng/g for tissues, food or faeces to 0.45 µg/l for urine (Sunderman *et al*, 1984; Sunderman, 1988). Greater analytical sensitivity (1 mg/l in biological media) can be achieved by DPASV using a dimethylglyoxime sensitised mercury electrode (Ostapczuk *et al*, 1983). DPASV techniques are cumbersome and time consuming.

The above routine procedures do not permit identification of individual nickel compounds. Assessment of individual nickel compounds, especially as components of complex mixtures, necessitates procedures such as X-ray diffraction and would not be feasible for routine monitoring (IARC, 1990).

1.2. COBALT

Cobalt can be analysed very easily by AAS in an air/acetylene flame. As there may be interferences with Ni, the 240.7 nm wavelength is the most appropriate with a detection limit of 0.006 µg/ml (Welz, 1983).

McPherson (1965) showed that analysis of Co is not hampered by the presence of 200 µg/ml Cr, Ni and W, 1,000 µg/ml Cu and Mo, 500 µg/ml Si, 200µg/ml Mn and V, 100 µg/ml Ti as well as 50 µg/ml P and S. Simmons (1973) has chelated Co with 2-nitroso-1-naphtol and extracted the complex out of plants with chloroform. Chloroform was afterwards evaporated and the residue analysed by AAS.

Welz (1983) reviewed other analytical techniques.

1.3. CHROMIUM

The voluminous literature on analysis for chromium has been reviewed by US-EPA (1978), WHO-IPCS (1988) and IARC (1990). Most instrumental

procedures are not specific for the oxidation states of chromium and are suitable for total chromium determinations only, unless accompanied by prior separations or supportive qualitative analyses. The reagent *sym*-diphenylcarbazide forms a violet complex with chromium (VI) but not with other chromium compounds, and the stability of the colour contributes to the high sensitivity of the analysis of soluble chromates. Interfering, reducing or oxidising substances, if present in the sample, must be taken into account, since they tend to cause erroneous results during sampling, sample storage and preparation and spectrometric measurement (NIOSH, 1975). The chromium content of single particles can be determined by electron microscopy combined with X-ray micro-analysis. Electron spectroscopy can be used to measure the valency state of chromium in thin surface layers of solid samples (Lautner *et al*, 1978).

The instrumental methods used are AAS (Welz, 1983), ICP (Welz, 1980), EAAS (Kettrup *et al*, 1985) and Neutron activation analysis (NAA) (Keller, 1980).

The sensitivity of instrumental analysis for the determination of chromium does not present any problems for concentrations in the mg/kg range. On the other hand, the sensitivity of instrumentation for the determination of chromium in the ng or $\mu\text{g/kg}$ is severely limited and no method is entirely satisfactory (Seeling *et al*, 1979). The biologically active concentrations are near the detection limits of the most sensitive methods, such as NAA or AAS. The analyses should always be controlled by the use of a certified reference material with a matrix composition similar to that of the material to be analysed.

The following supplementary problems may arise in the analysis of chromium:

- contamination
- loss through volatilisation (Kotz *et al*, 1972)
- formation of refractory compounds during sample preparation.

Contamination is a serious problem when low concentrations are present in the sample. Dust in the laboratories may contain up to 700 mg/kg of Cr (Mertz, 1969).

It is also important in any study of toxicological effects of chromium, to distinguish analytically between the trivalent and hexavalent forms. This can be accomplished by dithiocarbamate chelation and methylisobutylketone extraction prior to oxidation. Only the hexavalent chromium remains after this process (Feldman *et al*, 1967; Cresser and Hargitt, 1976; Bergmann and Hardt, 1979; Joschi and Neeb, 1980).

2. ANALYTICAL PROCEDURES TO DETECT NICKEL, COBALT AND CHROMIUM IN CONSUMER PRODUCTS

Wells (1956) only mentioned that the samples of six detergents powders were analysed by "spectrographic analysis".

Nater (1963), Feuerman (1971) and Weiler and Ruessel (1986) used a photometrical method for the determination of chromate content in consumer products. Preparation was with diphenyl carbacide and sulphuric acid solution and other chemicals such as nitric acid, perchloric acid and perhydrol. The extinction at 543 nm was determined on a Zeiss Spectrophotometer.

Kalveram and Forck (1977) only mentioned that the analyses of Cr and Ni in consumer products were made by AAS.

For the analysis of Cr, Ni and Co in detergents Wahlberg et al (1977) used a Perkin-Elmer 303 Atomic Absorption Spectrophotometer with three-slot Belling burner, Intensitron multi-element lamp and Hitachi-Perkin-Elmer Recorder 159. Ebner et al (1978) used a similar method for the determination of Cr and Ni. They used a Perkin-Elmer, Model 300 with a graphite oven baseline corrector HGA 72 and underground compensator. For the detection of the elements Cr and Ni a multi element hollow cathode activated by 30mA lamp current was used. The wavelengths for Cr was 357.8 nm, and for Ni 232.0 nm. The conditions in the graphite furnace were as follow: For drying of the sample 100°C (15 sec), for ashing from 600 to 800°C (30 sec), and for atomization 2,600°C (20 sec).

Barriere et al (1979) used AAS with the help of a Perkin Elmer 300 S for the detection of nickel in detergents. They dried the samples at 100°C (45 sec), ashed at 1,000°C (30 sec) and atomized at 2,659°C (11 sec). The measurement was made at a wavelength of 232 nm.

Lachapelle et al (1980) determined the chromium content of a liquid bleach by flameless AAS. The sample to be analysed was diluted (50/50 V/V) with 2.5% HNO₃. Three 2 ml portions of this solution were placed in polyethylene tubes; to two of these tubes was added 50 µl of freshly prepared standard solution containing 1 and 2 µg Cr/ml 2.5% HNO₃, respectively. To the third tube was added 50 µl of 2.5% HNO₃; 20 µl of each final solution was injected into the graphite oven and the concentration of the unknown solution was calculated by reference to the signals of the internal standards. A Perkin Elmer Model 420 AS-I atomic absorption spectrophotometer with a model HGA 76 B graphite furnace atomiser was used. Instruments settings were: hollow cathode 25mA; visible background corrector, slit 0.7mm, wavelength 357,8 nm, drying 10 sec at 100°C (rate 3; 14,85°C/sec) progressive increase of temperature (rate 1 x 30; 28,8°C/sec) up to 700°C, ashing 5 sec at 700°C (gas stop) and atomization at 2,500°C for 5 sec (gas stop). The signal was recorded on a

Perkin Elmer Model 165 recorder (10 mV scale; chart speed 60 mm/min). The concentrations are expressed in $\mu\text{g/l}$.

Kokelj *et al* (1984) used a Perkin-Elmer 5000 with HGA 500 and measured the quantity of chromium at a wavelength of 337.9nm. The steps of temperature were 120°C (drying), 1,200°C (mineralisation), and 2,700°C (atomisation). The steps of preparation of this method were described by Nava *et al* (1987) in detail. The quantitative analysis was made by atomic absorption spectrometry (Perkin-Elmer AAS Model 5000) with a graphite oven baseline corrector (HGA 500) and autosampler (AS 40).

Mueller (1985) carried out the analysis of Ni, Cr and Co by flameless atomic absorption spectrometry (Perkin-Elmer 3030) directly from the solution without any admixture.

Vilaplana *et al* (1987) determined the content of Co and Ni in the 30 most popular domestic detergents and cleaning products in Spain by AAS with a graphite camera.

Hostynek and Maibach (1988) described the determination of chromium in US consumer bleach as follows: For preparation, to 50 g of sample was added 10ml of 30% hydrogen peroxide to decompose the bleach, followed by 1ml concentrated hydrochloric acid. The sample was taken to a final volume of 65ml. The reagents used did not contribute to the blank. Standards were prepared in a matrix as described above. Measurements were made on an Instrumentation Laboratories Video 12 atomic absorption spectrophotometer using deuterium background correction for optimal sensitivity.

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APPENDIX 5

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