

Dermatological Toxicity of Hexavalent Chromium

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Hexavalent chromium causes two types of dermatological toxicities: allergic contact dermatitis (ACD) and skin ulcers. This report reviews the etiology, prevalence, pathology, dose-response, and prognosis of both of these reactions. Reports in the literature indicate that repeated exposure to hexavalent chromium in concentrations of 4–25 ppm can both induce sensitization and elicit chromium ACD. Exposure to 20 ppm hexavalent chromium can cause skin ulcers in non-sensitized people. The prevalence of chromium sensitivity in cement workers, exposed to 10–20 ppm hexavalent chromium for years, is approximately 4–5%. Chromium ACD can be a chronic debilitating disease, perhaps because chromium is ubiquitous in foods and in the environment and is difficult to avoid. Due to the high rates of sensitization in populations chronically exposed to chromium and the chronic nature of chromium ACD, some investigators recommend reducing the hexavalent chromium concentrations in consumer products, such as detergents, to less than 5 ppm.

Keywords Allergic Contact Dermatitis, Minimum Elicitation Threshold, Skin Ulcers

INTRODUCTION

Chromium is ubiquitous in the environment. It can be found in pigments, chrome-plated metals, tanned shoe leather, cement, detergents, and industrial chromium waste dumps. Following dermal exposure, chromium causes two types of dermatological toxicity. The most widely known reaction is sensitization and elicitation of allergic contact dermatitis (ACD). However, chromium also causes an irritation reaction that may progress to ulceration of the skin. This report reviews the etiology, prevalence, pathology, dose-response, and prognosis of both of these reactions, with an emphasis on concentrations of chromium that could be considered reasonable for human exposure.

The focus of this review is hexavalent chromium, Cr(VI), since trivalent chromium, the naturally occurring valence of this metal, has significantly lower dermal toxicity than does the hexavalent form. In general the trivalent forms of chromium diffuse through the skin at a much lower rate than hexavalent forms (Samitz et al., 1967), which may account for its lower dermatological toxicity. However, once hexavalent chromium penetrates the skin, it is reduced to the trivalent form (Polak, 1983). It is the trivalent form that binds to the immune cells of the skin, and

this is most likely the form ultimately responsible for dermal toxicity.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) is an immunologic reaction of the skin that occurs following exposure to environmental allergens. As reviewed by Belsito (2000, 2003), the susceptibility to develop allergic contact dermatitis is most likely genetically acquired. As shown in Figure 1, every time that an individual is exposed to an antigen (center of Figure 1), there is a clonal expansion of T-helper cells that, together with the antigen-presenting Langerhans cells (LC) and surrounding keratinocytes (KC), respond by producing inflammatory mediators. Initially, the number of responding T cells is insufficient to produce a clinical response (subclinical sensitization phase). It is only with repeated exposure to the potential allergen that clinically apparent disease occurs. Nonetheless, once an individual becomes sensitized to a given material, this sensitization remains for life.

PROGNOSIS

Individuals sensitized to chromium tend to suffer from a persistent dermatitis (Fregert, 1975), which is in contrast to individuals who are allergic to allergens more easily avoided. Fregert (1975) followed 14 chromium allergic individuals over a 10-year period. Among individuals with chromium allergy, 7%

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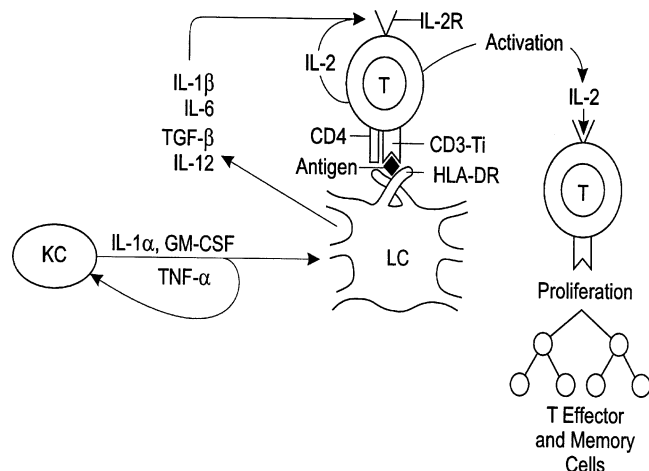


FIG. 1. An antigen (center of figure) combines with Langerhans cells (LC) and keratinocytes (KC). The subsequent interaction with T-helper cells (T) produces inflammatory mediators. (From the collection of Donald V. Belsito, MD, with permission.)

remained free of disease during that time, 43% had intermittent episodes of clinical disease, and 50% had chronic disease. The social and economic impact of this prolonged dermatitis was described by Burrows (1983). Breit and Turk (1976) stated, "The review of the available literature shows that the prognosis of the dichromate allergic patient is poor, taking into account his medical and social outcome. To improve the situation the prevention of sensitization would be the best solution; this would mean the strict avoidance of prolonged contact with dichromate-containing material" (p. 350). In response to this problem, many investigators have attempted to identify nonsensitizing levels of these metals, and some European Economic Union (EEU) countries have adopted restrictions regarding the concentration of chromium that can be contained in various consumer products.

Treatment of established ACD is primarily designed at prevention of future exposure. In the case of some allergens, such as metals and their salts, avoidance can be difficult. This is particularly true since metallic items are typically not labeled as a component in consumer products and are ubiquitous in the environment. Furthermore, trace levels of metals such as chromium are part of the normal diet, and are capable of eliciting allergic reactions in sensitized individuals (Veien, 1989; Veien et al., 1994).

INCIDENCE AND PREVALENCE OF CHROMIUM ACD

In order to evaluate reasonable levels of hexavalent chromium to which humans can be exposed, it is necessary to understand the incidence and prevalence of adverse dermal reactions to chromium. While Cr(VI) is widely recognized as one of the more common human sensitizing agents, the exact prevalence of chromium sensitization is not known. Estimates reported in the literature vary 100-fold, ranging from

0.08% (Proctor et al., 1998) to 7% (Burrows, 1983), depending on the population studied. Interpretation of these estimates requires an understanding of the methods used by the researchers and the definition of prevalence as it relates to chemical sensitization.

The prevalence of chromium sensitivity is the percent of the population who are already sensitized and who could potentially react to chromium in the environment. However, the prevalence rates of chromium sensitivity in any population will change in a typical dose-response manner: The prevalence rates will be higher in populations exposed to greater concentrations of chromium.

Comparison of data from cement workers with data from general population studies demonstrates the increased prevalence of chromium ACD in this population. Cement workers are chronically exposed to 10–20 ppm of hexavalent chromium in a highly alkaline medium (Stern et al., 1993), although cement is diluted > 1:1 prior to use, reducing the Cr(VI) concentration. Table 1 shows that the prevalence of chromium ACD in cement workers averages 4–5%. This is much higher than the prevalence rates reported for general European populations of around 0.5%, as discussed further later in this article. Furthermore, this prevalence rate represents the percentage of chromium-allergic individuals who were working with cement at the time of the study. It does not reflect workers who may have become allergic and who sought another line of work.

Interestingly, in some Asian and less well-developed countries, very high rates of chromium sensitization have been reported: Singapore, 40% (Goh et al., 1986); Taiwan, 13% (Guo et al., 1999); and Poland, 23% (Kiec-Swierczynska, 1990). Although the reason for these high rates of sensitization is not known, workers in these countries typically have less freedom to seek another type of work. Additionally, cement in these countries may contain more chromium than cement in Western countries (Stern et al., 1993).

Regarding prevalence rates in the general population, several population-based studies are available from Europe; however, there are no data regarding the incidence and prevalence rates of chromium ACD in the United States, despite the ability of U.S. health-care providers to test for chromium sensitivity. Furthermore, the European rates could vary significantly from that in the United States due to possible differences in the genetic composition of the population, chemical exposure patterns, etc. A higher general prevalence rate of chromate dermatitis in the United States might be expected compared to European Economic Community (EEC) countries, given the fact that ferrous sulfate is added to cement in many European countries to reduce the level of hexavalent chromium, while no such protective measures are performed in the United States.

One European study, Lantinga et al. (1984), assessed the prevalence of chromium ACD in the general adult population in one defined area of the Netherlands from 1979 to 1982. Of 1992 individuals examined, 9 (0.45%) were found to be sensitive to chromium. However, interpretation of this study is limited in

that 1781 of the 1992 individuals were not tested to definitively determine chromium sensitivity.

Perhaps the best point prevalence study of allergic reactions to chromium was that performed by Nielsen and Menne (1992), who tested 567 randomly recruited individuals living in Glostrup, Denmark. Overall, in this Danish population, 0.53% of individuals were sensitized to chromate; among males, the prevalence was 0.7%. Due to these high rates of sensitization, the EEC banned the use of trivalent chromium salts in cosmetic products, such as eye shadow (EEC Directive, 1976), due to the possibility of contamination with hexavalent chromium and the possibility of chromium sensitization following skin absorption of the trivalent form from the very thin skin around the eye. In addition, some investigators have suggested restricting hexavalent chromium in noncosmetic consumer products, such as detergents, to <5 ppm (Basketter, 1993).

Although, as previously stated, there are no prevalence data for the U.S. general population, there are data regarding the prevalence rates for Cr(VI) ACD in patients with dermatitis, published by the North American Contact Dermatitis Group (NACDG). NACDG is a multicenter group of U.S. and Canadian physicians that periodically reports the rates of allergic reactions to the various chemicals screened by the group. The data collected over the past 28 years are summarized in Table 2. The prevalence rate for chromium sensitivity in individuals with suspected contact dermatitis will be greater than that for the general population.

Proctor et al. (1998) attempted to estimate the prevalence of allergic contact dermatitis in the general U.S. population by utilizing the NACDG data as well as two contemporaneous Dutch studies, one of which looked at prevalence in the general population and the other at prevalence in a diseased population. The authors utilized the Dutch studies to determine a ratio between the prevalence of chromium ACD in patients with eczema to the prevalence of chromium ACD in the general population, i.e., a clinical population to general population prevalence ratio. In doing so, they relied on the work of Lantinga et al. (1984), who reported a prevalence rate of 0.45% in a random sampling of the general Dutch population, and data from Van Ketel (1984), who determined that 5.8% of 1779 Dutch patients with suspected

contact dermatitis were allergic to chromium. This produced a general to clinical prevalence ratio of .078. Using the clinical chromium ACD prevalence data from the NACDG, Proctor et al. (1998) calculated a prevalence rate of 0.08% for the general U.S. population.

However, Proctor et al. made several errors in their analysis. Chief among these is that they misunderstood the dermatological classification of a positive allergic patch test reaction as "not relevant." Dermatologists may classify an allergy as "not relevant" to a current dermatitis problem if, for example, the patient has no current exposure to this allergen. As a result of their misunderstanding, these authors assumed that the NACDG chromium-allergic patients whose chromium allergy was classified as "not relevant" were falsely diagnosed with allergy. The authors then excluded these patients from their calculation of the general population to clinical population ratio, resulting in an erroneous low ratio.

Furthermore, as previously mentioned, the Lantinga et al. (1984) study that Proctor et al. (1998) relied on for the prevalence of chromium sensitivity in the general Dutch population failed to patch test 89.4% of their patients to confirm their allergy. More reliable data can be derived from the Danish studies performed by Torkil Menne's group in the late 1980s.

In the population study of Glostrup, Denmark, Nielsen and Menne (1992) detected a 0.53% incidence rate of chromium allergy among a randomly recruited population of 567 individuals, all of whom were patch tested. During this same time period, Christophersen et al. (1989) determined that 4.3% of 2166 patients presenting with clinical disease were allergic to chromate. These more reliable studies yield a general to clinical ratio of 0.12. Using this ratio and the current 4.3% clinical prevalence rate of chromate allergy determined by the NACDG (Table 2) yields an estimated prevalence rate of 0.52% for allergy to hexavalent chromium in the population of the United States. This number is consistent with those previously reported by Hostynek

TABLE 1
Chromate dermatitis in cement workers

Country	Percent of workers screened
Italy	1.3
Sweden	4.9–5.9
Norway	5.5–7
Northern Ireland	3.5
Australia	5.2

Note. Data abstracted from Burrows (1983).

TABLE 2
Prevalence rates of ACD to Cr(IV) in dermatitis patients as reported by the NACDG

Year	Sample size	Prevalence rate (%)	Reference
1972	1200	7.6	Rudner et al. (1973)
1984–1985	1138	5.2	Storrs et al. (1989)
1985–1989	3949	2.4	Nethercott et al. (1991)
1992–1994	3497	2.0	Marks et al. (1995)
1994–1996	3106	2.0	Marks et al. (1998)
1996–1998	3440	2.8	Marks et al. (2000)
1998–2000	5833	5.8	Marks et al. (2003)
2001–2002	4913	4.3	Pratt et al. (2004)
2003–2004	5142	4.3 ^a	

^aPreliminary: D. V. Belsito, MD, member and immediate past president, NACDG.

and Maibach (1988) of less than 1%, by Paustebach et al. (1992) of 0.7%, and by Nethercott (1990) of 0.6%.

The 0.52% prevalence rate calculated in this article is significantly larger than the 0.08% estimated in the Proctor et al. (1998) paper, by one order of magnitude. This is due not only to errors just described, but also to the fact that Proctor et al. (1998 p. 179) used NACDG 1992–1994 data, when the rate of allergic contact dermatitis is a threshold response; single or repeated exposure to low levels of a sensitizer may not produce an allergic contact dermatitis if the threshold is not reached. As can be seen in Table 1, this rate has been creeping upward since 1996. In retrospect, the decline was probably due to the economic factors of the late 1980s and early 1990s (i.e., the decreased rate of new construction and therefore the decreased number of workers exposed to chromium in cement) in the United States rather than to any improved industrial safety standards or declining prevalence rate. As discussed elsewhere in this article, the induction of ACD to chromium requires years of chronic, low-grade exposure to Cr(VI). When a lag time of 5–10 years is factored in, the decline in the incidence rate of ACD to Cr(VI) in the 1980s, as noted in Table 2, may be explained by the economic recession of the late 1970s and early 1980s causing fewer workers to be exposed to chromium in, for example, chromium-containing cement. The very recent increase in the rate of ACD to Cr(VI) may be due to the economic recovery in the 1990s and the subsequent exposure of more workers to chromium materials. It appears, as would be logically expected, that the prevalence of chromium contact dermatitis in the general population is related directly to the number of people exposed to chromium, following a lag time.

It is worth noting that one study conducted in the United States did attempt to determine the prevalence of chromium ACD in a specific population. Fagliano et al. (1997) set out to determine the prevalence of chromium ACD in individuals who were living or working in the vicinity of chromium industrial waste sites in Hudson County, NJ, from January 1992 through March 1993. These chromium waste sites were in close proximity to residential and commercial areas, and some were unofficial play areas for children in the past.

Unfortunately, the Fagliano study has numerous methodological errors. In fact, Fagliano et al. (1997) did not document any cases of chromium ACD among the approximately 1700 people screened. Even if the prevalence of chromium sensitivity is only 0.52% in Hudson County, as it may be for the general U.S. population, which includes individuals not exposed to chromium, then, statistically speaking, this study should have found approximately 9 cases. The fact that not even one case was documented raises concerns that the screening and evaluation methods were not adequate to detect chromium ACD.

Specific problems with the methods used by Fagliano et al. (1997) include the fact that they only evaluated volunteers who responded to advertising, and did not attempt to recruit long-time residents or workers, or even document the length of time that their volunteers had lived and/or worked in chromium contam-

inated areas. Given that induction of allergic contact dermatitis to chromium typically requires months to years of low-level exposure, it is difficult to know whether the study population was exposed to chromium long enough to develop ACD.

Furthermore, subjects were given screening physical examinations by physicians who were not dermatologists. These physicians determined whether subjects were referred to a dermatologist for further examination. Part of the screening criteria included asking the subjects whether they had “chronic dermatitis.” However, this criterion may have screened out 50% of individuals suffering from ACD to chromium. Fregert (1975) studied 14 chromium allergic individuals over 10 years, and found that, with attempted avoidance of contact with chromium, 7% were free of disease, 43% had intermittent symptoms, and 50% had chronic dermatitis.

In addition, Fagliano et al. (1997) state that participants were not referred for follow-up examination by a dermatologist if “there was another known cause [of the symptoms] unrelated to chromium exposure.” Presumably this means that if a participant suffered from dermatitis but informed the examining physician that he or she was previously diagnosed with, for example, nickel ACD, the physician did not refer the participant for further examinations by a dermatologist. If this is the case, then potential cases of chromium ACD would have been undetected, as it is not unusual for a patient to be allergic to more than one metallic allergen (Lammintausta et al., 1985; Zaczekiewicz and Czerwinska-Dihm, 1994; Ruff and Belsito, 2006).

Also, approximately 52% of participants were screened during the fall and winter months (Fagliano and Savrin, 1994), when people typically spend less time outside. The failure of Fagliano et al. (1997) to analyze their data for seasonal effects may have had a significant impact. The Tokyo Metropolitan Government Bureau of Sanitation study (1978–1987) compared the incidence of allergic contact dermatitis and eczema of the hands in 259 housewives living in a neighborhood contaminated with unknown levels of hexavalent chromium to 177 age and sex matched controls. A statistically significant increase was observed in the summer (but not the winter) months, when contact with the external environment is greatest (data summarized in Bagdon and Hazen, 1991).

Thus, due to the apparent methodological problems, the results of the Fagliano et al. (1997) study cannot be used as an accurate assessment of the prevalence of chromium ACD in Hudson County, NJ.

INDUCTION OF ALLERGIC CONTACT DERMATITIS FOLLOWING DERMAL EXPOSURE

In order for ACD to develop, a genetically susceptible individual must have biologically significant, and often repeated, contact with the allergen. While Paustebach et al. (1992) stated that “Allergic contact dermatitis is a threshold event. Single or repeated exposure to low levels of a sensitizer may not produce an allergic contact dermatitis if the threshold is not reached,” Friedmann (1990) stated in his review of the dose/response

induction of allergic contact dermatitis to dinitrochlorobenzene and the effects of subclinical sensitivity that "An apparently ineffective sensitizing stimulus is ... registered immunologically ... [and results in] enhanced subsequent responses to the same antigen" (p. 186). This progressive subclinical induction of disease is consistent with the multitude of clinical observations that induction of chromium allergy takes months to years of exposure to low levels of the allergen (Hovding, 1970; Walsh, 1953). Thus, while the acute induction of allergic reactions to hexavalent chromium (in 2–6 weeks following initial exposure) under laboratory conditions requires concentrations of 0.5–2% (Wass and Wahlberg, 1991; Kligman, 1966; Hicks et al., 1979), and exposure to lower concentrations does not produce clinically apparent reactions in this shortened time frame, one cannot conclude, as Paustenbach et al. (1992) have, that these lower chromium concentrations have no effect. The literature discussed in detail next clearly shows that lower concentrations of chromium can indeed induce sensitization, if exposure occurs for a longer period of time. Furthermore, while some authors have stated that the lowest chromium concentration to elicit ACD in a chromium-sensitive individual is much lower than the chromium concentration necessary to induce chromium sensitization in a nonsensitized individual, this does not appear to be the case. Increasingly, ACD researchers realize that the concentrations for inducing and eliciting ACD are probably the same with exposure scenarios that happen in "real life," as opposed to those in an artificial laboratory situation.

The following data illustrate this point. In a Spanish study, Quinones and Garcia-Munoz (1965) found a 90.5% correlation between detergent dermatitis and allergic reactions to hexavalent chromium. An analysis of 20 leading consumer detergents revealed hexavalent chromium levels ranging from 2.1–6.2 ppm, with an average of 4.3 ppm. Similarly, Feuerman (1971) found 229 of 250 (92%) Israeli housewives with hand dermatitis were allergic to hexavalent chromium. In the absence of other known sources of contact with hexavalent chromium, the authors performed an analysis of the levels of hexavalent chromium in the most common powdered detergents, which showed a range of 0.4–23.2 μg of hexavalent chromium per gram of detergent (mean = 5.4 μg /g). Of note, these powdered products were likely diluted 50- to 100-fold prior to use, although the authors of these studies give no information regarding method or length of exposure to the detergents.

As discussed in detail later, cement dermatitis has also been strongly correlated with allergic reactions to hexavalent chromium. As reviewed in Stern et al. (1993), the soluble hexavalent chromium concentration in cements from different countries tends to cluster around 10–20 ppm. Thus, low levels of hexavalent chromium apparently induced sensitization to chromium in these individuals, and elicited chromium ACD in them with continued exposure. Since cement is also diluted with water prior to use, these data suggest that the chromium concentration necessary for induction of sensitization and elicitation of chromium ACD is the same or lower than the chromium concentrations

in detergents (average 5 μg /gram or 5 ppm) and in cement (10–20 ppm).

Given the ability of low levels of hexavalent chromium to sensitize significant number of chronically exposed individuals, Basketter et al. (1993) have recommended, as a standard, that hexavalent chromium be present at <5 ppm in noncosmetic consumer products, with an ultimate goal of <1 ppm.

IRRITATION REACTIONS AND SKIN ULCERATION

While chronic exposure to low concentrations of hexavalent chromium results in allergic contact dermatitis, exposure to presumably higher hexavalent chromium concentrations, or to lower concentrations under suitable conditions (abraded skin, high ambient temperature/humidity, etc.), may result in "chromium ulcers" or "chrome holes." These ulcers develop most often on the extremities of workers exposed to cement and the nasal septum of lithographers and other workers exposed to chromic acid vapors. Furthermore, among workers exposed to hexavalent chromium in whom ulcer formation is the dominant cutaneous effect, incidence rates of allergic contact dermatitis to chromium seem to be reduced (Walsh, 1953). This paradox most likely results from the fact that exposures that produce an ulcer destroy the immunologic capability of the skin to respond, thus preventing an allergic response.

Walsh (1953) describes chrome ulcers as "a punched out lesion, 2 to 5 mm in diameter, with a raised collar-like indurated border several millimeters wide. It tends to take the shape of the preceding break in the skin. There is minimal inflammation, and the lesions are relatively painless, except when near a joint or subject to trauma. They usually heal, leaving a depressed atrophic scar, although hypertrophic scarring has been seen. No instance of malignant degeneration has been reported in a chrome ulcer or in a septal perforation. There apparently is no increased tendency on the part of workers in whom these lesions develop to become sensitized to chromates. . . . The ulcers apparently are due to a toxic, necrotizing action of the chromate ion on living tissue, independent of its sensitizing properties" (p. 8). Thus, chrome ulcers are a separate and distinct reaction from allergic contact dermatitis (ACD). Allergic contact dermatitis occurs in people sensitized to chromium. In contrast, chrome ulcers can and do occur in nonsensitized people who remain nonsensitized to chromium.

Cuadra et al. (1982) reported histopathological findings in biopsies from two chrome workers with dermal chrome ulcers. Neither individual was sensitized to chromium as evidenced by negative International Standard Series skin tests. Both cases had a focal loss of the epidermis with marked hyperplasia of the margins of the ulcer. Both also had infiltration of the sweat glands, which the authors consider a notable finding, particular to chromium.

DaCosta et al. (1916) reported similar findings. The histopathology report from a leather worker's chrome ulcer states that "The floor of the ulcer is made up of nests of polynuclear leucocytes, areas of hemorrhage and cellular de-

bris. Sections of sweat glands, or sebaceous glands, and of hair follicles are present, and in the immediate vicinity of the structures are accumulations of polynuclear leucocytes and some few round cells indicating a marked inflammatory condition" (Da-Costa et al., 1916, p. 162).

The minimum concentration of Cr(VI) and length of exposure needed to produce chrome ulcers are not known, and will likely remain unknown, given the ethical considerations regarding such testing on humans. However, Walsh (1953) conducted a dose-response study of the concentrations and lengths of exposure to hexavalent chromium necessary to produce dermatological chrome ulcers in a volunteer who was not sensitized to chromium. The results showed that concentrations of sodium dichromate as low as 0.005% (20 ppm Cr(VI)), when applied on a patch to a superficial scratch for 8 hours per day for 3 days, produced a chrome ulcer 1 by 2 mm in diameter that took 2 weeks to heal. Thus, under the correct experimental conditions (abrasion and occlusion), levels of Cr(VI) that reportedly induce ACD can also induce ulceration. The mechanism by which Cr(VI) produces chrome ulcers is not known. However, recent data demonstrating that Cr(VI) disrupts the actin cytoskeleton and induces mitochondria-dependent apoptosis in dermal fibroblasts could show a potential mechanism by which it induces cutaneous ulcers (Rudolf et al., 2005).

ELICITATION OF ALLERGIC CONTACT DERMATITIS

Patch-Test Studies

Numerous studies have been published evaluating the threshold dose of hexavalent chromium needed for the elicitation of allergic contact dermatitis by patch testing. Some authors have attempted to use this information to determine concentrations of chromium that could be considered "safe" for environmental exposure, i.e., concentrations that will not result in elicitation of ACD in most chromium-sensitive individuals. However, patch testing is an artificial situation in which the chemical is placed onto normal skin (typically the thicker skin of the upper back) under occlusion for a period of 48 h. The effects of occlusion increase the rate of responsiveness by increasing the absorption of the applied materials. This allows for the elicitation of the allergic reaction within 2–7 days following a single application of the chemical. In contrast, under real-life conditions, an individual may be exposed to this chemical numerous times during the course of the day on thinner skin, which may or may not be clinically normal. In the aggregate, however, the increased effect of occlusion may be counterbalanced by the single application to normal skin. However, as will be seen, numerous factors influence the results of patch testing.

Utilizing patch tests to determine the threshold for elicitation of chromium allergy, Zelger (1964) found that 3 of 33 individuals known to be allergic to hexavalent chromium (9%) reacted to 10 ppm chromium as sodium chromate (pH 11.7). Interestingly, when these same individuals were tested to 10 ppm chromium as potassium dichromate (pH 1.5), none of the 33 individuals

reacted. Zelger concluded that the basic pH of the sodium chromate enhanced penetration of the hexavalent chromium allergen. Others have subsequently confirmed this observation. Gammelgaard et al. (1992) noted that as the pH of the medium increased from 6.8 to 10.0, the absorption of hexavalent chromium through the skin increased 100-fold. Thus, in assessing the elicitation threshold for chromium allergy, the pH of the exposure medium is important.

Calnan (1962) found little change in the penetrability of hexavalent chromium over a pH range of 7.7 to 10.1. However, at pH levels greater than 10.1, absorption of hexavalent chromium into the skin was significantly increased. Gammelgaard et al. (1992) noted that when all other variables were held constant, the penetration of hexavalent chromium through full thickness human abdominal skin *in vitro* increased 100-fold over the pH range 6.8 to 10, and approximately 2.5-fold over the pH range 8.8–10. Wahlberg (1968, 1973) noted similar results.

The mechanism by which pH levels greater than 10 enhance penetration of hexavalent chromium is unclear. A shift in the dichromate to the monochromate form of hexavalent chromium with increasing pH results in an increased number of ions (approaching two times) in solution, which might account for enhanced penetration. However, one cannot discount a subclinical disturbance of the epidermal barrier induced by an irritant effect of solutions with a pH above 10. In the Gammelgaard et al. (1992) study, enhanced penetration of water, as well as hexavalent chromium, was noted across excised abdominal skin as the pH of the vehicle increased, suggesting a nonspecific irritant effect. However, irritation alone did not appear to account for the entire enhancement in chromium penetration.

Andersen et al. (1991), as well as many other authors, have demonstrated enhanced irritation with increasing pH. Indeed, Tsai and Maibach (1999) found that water at pH 7.5 was significantly more irritating than water at pH 5.5. The paradox that water at a neutral pH is more irritating than at a slightly acidic pH can be understood when it is appreciated that the skin's pH normally ranges from 4.2 to 5.5.

In addition to pH, the amount of time that the patch remains applied to the skin (and the vehicle used to dissolve the allergen) can affect the results. In their studies to assess the feasibility of a patch test application time of 6 hr, Kosann et al. (1998) evaluated 12 volunteers previously determined to be allergic to Cr(VI) based upon a 48-h patch test using 884 ppm Cr(VI) in petrolatum. As delineated in Table 3, 11/12 volunteers again reacted to concentrations of Cr(VI) up to 884 ppm in water when applied for 48 h, while 1/12 did not react even to a concentration as high as 1768 ppm Cr(VI) in water. When these same subjects had the patch tests applied for only 6 h, 3/12 remained reactive at concentrations of Cr(VI) up to 884 ppm in water, 4/12 reacted only at a 1768 ppm level of Cr(VI) in water, and 5/12 did not react at any of the tested levels. Of note, in their *in vitro* study of percutaneous absorption of hexavalent chromium into the skin, Liden and Lundberg (1979) noted more rapid percutaneous absorption of Cr(VI) when petrolatum is used as the vehicle, a fact that

TABLE 3

Minimum Cr(VI) concentration in water to elicit ACD with application for 6 or 48 h

Cr(VI) concentration (ppm)	6 h (<i>n</i> out of 12 subjects)	48 h (<i>n</i> out of 12 subjects)
28	0/12	1/12
110	0/12	1/12
220	1/12	4/12
440	0/12	1/12
884	2/12	4/12
1768	4/12	0/12
No reaction	5/12	1/12

Note. Data from Kosann et al. (1998).

might explain why 1/12 subjects failed to respond to testing with Cr(VI) levels as high as 1768 ppm even when applied for 48 h. Furthermore, these same authors found that steady state limits for aqueously dispersed chromium absorption through normal back skin under the conditions of patch testing occurred around 5 h following application of 0.5% potassium dichromate (1768 ppm hexavalent chromium) to the skin of human volunteers and that absorption continued at this steady state level for up to 72 h. Thus, it is not surprising that using a shortened patch test time of 6 h resulted in fewer reproducible positive reactions in the volunteers evaluated by Kosann et al. (1998).

Finley et al. (2000) reviewed the Kosann et al. (1998) data and suggested that "prediction of a dermal allergic response resulting from short-term environmental exposures might be overstated if based on data from longer-term clinical exposures" (p. 122), i.e., patch tests. However, this assumption would be correct only if the exposures were equivalent. As previously discussed, in real life, individuals are repeatedly exposed to lower levels of the sensitizer concomitantly with other chemicals (sensitizers, irritants, etc.) on larger, and not necessarily normal, areas of skin that are often thinner and more absorptive than the skin of the back. In contrast, patch testing has been designed to detect sensitized individuals within a period of 2–7 days utilizing a single application of purified material to a limited area (less than 8 mm) of normal skin, under controlled conditions of occlusion, so as to minimize type 1 (false positive) and type 2 (false negative) errors. As pointed out by Cohen and Brancaccio (2000) in their rebuttal to the Finley et al. (2000) discussion of their data (published as Kosann et al., 1998), clinical patch testing does not attempt to replicate environmental exposure, nor is it the ideal model for assessing minimal elicitation thresholds (METs) for environmental exposure.

Nonetheless, analyses of patch test data yield interesting results. Utilizing a log-probit analysis of 9 patch test studies that evaluated ACD elicitation thresholds for hexavalent chromium at different pH levels, Stern et al. (1993) estimated a threshold for elicitation of allergic reactions to be 15 ppm of hexavalent chromium for 10% of the population and 7.6 ppm for 5% of the sensitized population. Eun and Marks (1990) found a simi-

TABLE 4

Endogenous and exogenous factors affecting elicitation thresholds for ACD

Endogenous	Exogenous
Application site	Vehicle
State of stratum corneum	pH
Follicular shunting	Exposure time
Epidermal thickness	Exposure area
Immunologic state of the host	Occlusion
	Ambient temperature
	Ambient humidity
	Concomitant exposures
	Sunlight exposure
	Medications

lar level in their study which utilized laser Doppler technology (rather than the naked eye) to assess for allergic reactions. These authors reported significant enhancement in local cutaneous blood flow following the application of 10 ppm hexavalent chromium.

To date, no dilutional patch test studies have identified an absolute no observable effect level (NOEL). This is not surprising, since, as mentioned above, the patch test technique relies on the use of exaggerated concentrations of a purified allergen so as to minimize type 2 errors when minute amounts of the allergen are applied once to small (less than 8 mm) areas of normal skin. Furthermore, allergic responsiveness is controlled by many variables and the threshold will wax and wane with these variables over time (Table 4).

Allenby and Goodwin (1983) demonstrated the ability of the threshold elicitation dose to vary over time. In their dose response study of hexavalent chromium allergy, 2 of 14 known chromate allergic patients reacted to 8.9 ppm hexavalent chromium. While the test sites were still active, one of these highly sensitive subjects was tested with decreasing concentrations of potassium dichromate ranging from 4.5 to 0.15 ppm. At that particular time, the threshold eliciting concentration for this subject was estimated to be between 1.2 and 0.6 ppm. Two years later, this same subject was retested with solutions containing 2.3, 1.2 and 0.6 ppm hexavalent chromium on normal back skin and no positive reactions were observed. Such variations in the threshold for elicitation of ACD are the norm. For the severely allergic individual under proper circumstances, the NOEL could be very low.

While parts per million are an appropriate unit for determining threshold concentrations for exposure to chromium that will remain in contact with the skin in liquid phase, elicitation thresholds for solid phase chromium exposure are best described in micrograms per square centimeter of skin. Friedmann (1990) first introduced this notion of exposure per unit area of skin and Finley et al. (1995) demonstrated its utility. In this latter study, the authors utilized 175 ppm hexavalent chromium that was constituted in a solid-phase patch-test material and presented to the

skin as either 0.88 or 0.13 μg of hexavalent chromium/ cm^2 of skin. Nine volunteers, previously determined to be allergic to chromate, were simultaneously tested with these two patches: 6 of the 9 volunteers exposed to the 0.88- $\mu\text{g}/\text{cm}^2$ patch reacted, while none of the volunteers responded to the patch containing 0.13 $\mu\text{g}/\text{cm}^2$. Utilizing this solid-phase patch-test device, impregnated with concentrations of hexavalent chromium ranging from 0.018 to 4.4 $\mu\text{g}/\text{cm}^2$, Nethercott et al. (1994) tested 54 patients known to be hypersensitive to chromium. One of 54 (2%) reacted to the lowest level tested (0.018 $\mu\text{g}/\text{cm}^2$) and 5 of the 54 (9%) reacted to the next lowest dose studied (0.088 $\mu\text{g}/\text{cm}^2$). As was found for patch studies utilizing liquid-phase allergen, a no-observed-effect level (NOEL) was not observed. Extrapolating their data, these authors determined a minimal elicitation threshold for 10% of the allergic population to be 0.089 $\mu\text{g}/\text{cm}^2$, although the authors did not determine the rate of release of hexavalent chromium from the solid-phase vehicle.

Wass and Wahlberg (1991) studied 5 chromate sensitive subjects who were patch tested with 12-mm chromated steel disks containing various amounts of hexavalent chromium, as determined by subsequent extraction using artificial sweat. All 5 volunteers reacted to disks that were determined to release $\geq 0.6 \mu\text{g}/\text{cm}^2$ of hexavalent chromium. Four of the 5 subjects reacted to disks that were subsequently determined to release $\geq 0.24 \mu\text{g}/\text{cm}^2$. One of 5 (20%) reacted to 0.04 $\mu\text{g}/\text{cm}^2$. Of note, in the Wass and Wahlberg study, chromated steel containing levels $\leq 0.003 \mu\text{g}/\text{cm}^2$ of hexavalent chromium, as assayed following extraction with synthetic sweat, did not induce dermatitis in any of the volunteers.

Immersion Techniques and Repeat Open Application Tests (ROAT)

As noted earlier, the patch test technique may not be the ideal test for proper identification of "real-life" elicitation thresholds. Thus, over the past two decades, numerous authors have advocated more life-like elicitation techniques such as the repeated immersion or the repeated open application testing (ROAT) techniques. In both, the allergen is applied for brief discontinuous periods, the application site is not occluded, and repeated applications of lower, more "realistic" concentrations of the allergen are used. However, even these methods have their limitations; chief among which are that the allergen is applied to normal skin under controlled conditions in the absence of concomitant chemical exposures.

The use of immersion to assess elicitation thresholds for hexavalent chromium was first reported by Fowler et al. (1999). According to the study protocol, 26 volunteers with known hypersensitivity to hexavalent chromium (minimal patch test elicitation thresholds ranging from 0.018 to 4.4 $\mu\text{g}/\text{cm}^2$) were to immerse one forearm for 30 minutes per day on 3 consecutive days in a solution containing 25 mg/L (25 ppm) hexavalent chromium (pH 9.5). The contralateral arm was to be immersed in the alkaline buffer only. Individuals with active eczematous

dermatitis were excluded from enrollment. Although the authors concluded that, based on their results, exposure to 25 ppm hexavalent chromium in the environment does not pose an allergic contact dermatitis hazard to chromium sensitized persons, a critical review of their findings suggests otherwise.

In the first phase of the Fowler et al. (1999) study, clinical evaluation of the immersed arms was performed by dermatologists who were blinded as to the treated sites. The results show that 14 of 26 (54%) of participants developed pruritus, erythema, papules, and/or vesicles, although the findings in 4 of these 14 were equivocal. However, 4 of the 10 subjects with unequivocal reactions did not complete the exposure protocol for unstated reasons. Two subjects underwent only 1 day of immersion, and this exposure resulted in a moderate degree of itching, erythema, and vesiculation in one of these two volunteers. The other volunteer had moderate level of itching and papules and a mild level of erythema and scaling. The other 2 of the 10 subjects underwent immersion for only 2 days. One of these had mild vesiculation, papules, erythema, pruritus, and scaling, and the other had mild papules, erythema, and pruritus. Furthermore, it is curious that 6 consecutive patients (numbers 8–13) had no reactions of any kind. Since this was a multicenter study, it would be helpful to know if all of these patients were from the same site, as this might suggest methodological explanations of one form or another.

Discounting the 4 patients with equivocal reactions, 10 of 26 (38.5%) developed signs and symptoms consistent with an allergic reaction and were eligible to enter Phase 2 of the study. In the second phase, the 10 volunteers who clearly reacted in phase 1 were asked to return approximately 1.5 months after phase 1 for participation in phase 2. In phase 2, chromium exposures to the forearm were to be similar to those in phase 1 and were to be followed within 24 hours by biopsies of any clinically involved skin. Among the potential 10 volunteers in phase 2, one (the patient who developed a moderate degree of symptoms after only 1 immersion in phase 1) was unable to return because of an injury. In addition, 4 of the individuals who reacted in phase 1 were excluded because of active ongoing dermatitis. Although the nature of the dermatitis was not described, it is of particular interest that, given the known tendency for allergic reactions to chromium to persist for prolonged periods of time despite avoidance (Fregert, 1975; reviewed in Burrows, 1983), 40% of the reactors in phase 1 had active dermatitis 1.5 months following exposure.

In the five patients who underwent phase 2 of the testing in the Fowler et al. study (1999), all 5 developed some degree of erythema and rash, and 4 of the 5 complained of moderate to severe itching. Of note, 2 of these 5 underwent immersion for only 1 day, and 3 for 2 days, before the onset of symptoms; none of the 5 completed the anticipated 3 days of immersion. Although the authors argue that the earlier induction of symptoms and an earlier resolution of disease in Phase 2 mitigate against the observed rash being allergic contact dermatitis, in fact, the earlier onset of allergic reactions is typical for "recall reactions," i.e.,

reactions that occur fairly soon after an initial reaction (reviewed in Belsito, 2003). Furthermore, the more rapid resolution could be accounted for by the fact that 2 of 5 patients only had 1 day of immersion, and the other 3 patients had 2 days; thus, the observation over 7 days for these 5 patients cannot be realistically compared to the observations over 7 days for the 24 patients reacting in phase 1, most of whom had 3 days of immersion.

The biopsies of all 5 patients were remarkably similar to each other. Edema of the epidermis (spongiosis) and dermal inflammation about the vasculature, hair follicles, and sweat ducts were seen in all 5. Spongiosis is the histopathologic hallmark of allergic reactions (reviewed in Belsito, 2003). Furthermore, as delineated by Waldorf et al. (1991), early allergic reactions are typically first manifest about the hair follicles. Thus, in the aggregate, a cutaneous reaction consistent with allergy was seen in all 5 subjects. Furthermore, in 3 of the 5 biopsies, epidermal necrosis (which was accompanied by a neutrophilic infiltrate in 2) was also seen. Such pathologic changes are consistent with the early phases of "chromium ulcers," an irritant effect (Da Costa et al., 1916; Cuadra et al., 1982).

Based upon our review of the Fowler et al. (1999) study, at least 10 of 26 (38%) of individuals exposed to 25 ppm hexavalent chromium developed dermatitis consistent with allergic contact dermatitis. In the 5 subjects in whom tissues were studied microscopically, areas of irritation (possibly early chromium ulceration) coexisted with areas consistent with ACD. It would therefore appear that exposure to 25 ppm hexavalent chromium in the environment would indeed pose an allergic (and possibly irritant) contact dermatitis hazard for both chromium sensitized and nonsensitized individuals. Furthermore, the authors themselves state that only chromium-sensitized volunteers were used in this study due to the "concern that the volunteers could be sensitized to Cr(VI) by the experiment." (p. 159) Given the previous discussion that hexavalent chromium levels in the 5–10 ppm range can indeed induce sensitization, this is a reasonable concern. The authors' statement that "Based on these data, concentrations of 25 to 29 mg/L [25 to 29 ppm] Cr(VI) in water can be considered the no-effect levels for ACD and irritant contact dermatitis for Cr-sensitized persons for nearly all plausible environmental exposures to standing water" (p. 160) is not consistent with the dermatological effects documented in their paper.

In another study using a combination of dilutional patch testing and repeat open application testing of 17 volunteers known to be allergic to hexavalent chromium, Basketter et al. (2001) found that 3 of 17 patients (17.6%) reacted to 10 ppm hexavalent chromium, and 1 of 17 (5.9%) reacted to 1 ppm hexavalent chromium, following a 48-h patch test on normal skin. The pH of these solutions was not given. When the test sites of these volunteers were subclinically irritated with a 1% solution of sodium lauryl sulfate (a common household detergent) prior to patch testing, 17% and 11.8% of the 17 volunteers reacted to 10 ppm and 1 ppm hexavalent chromium, respectively. In the second phase of this study, 15 of the 17 participants rubbed a small amount of a solution containing 1% sodium lauryl sulfate

and various hexavalent chromium concentrations in water, twice daily, for 1 week, to their antecubital fossae (elbow crease, the repeat open application testing technique). Three of the 15 (20%) had clinical evidence of an allergic reaction at 5 ppm hexavalent chromium.

The ability of low levels of hexavalent chromium to elicit dermatitis in sensitized patients was further demonstrated by Nielsen et al. (2000), who studied 3 patients with known hexavalent chromium allergy. In this study, participants were asked to immerse 1 finger in a solution of 10 ppm hexavalent chromium for 10 minutes per day, over a 1-week period. The pH of this solution was not stated. In all three patients, a significant flare of a vesicular (blistering) rash developed on the immersed finger.

Table 5 lists the minimum concentrations of hexavalent chromium reported to cause dermatological effects in the medical literature. Thirteen out of 14 studies show dermatological toxicity from exposure to hexavalent chromium from 4 to 25 mg/L (4–25 ppm). These results are remarkably similar, considering these studies used a wide range of methodologies and were conducted over decades in many different countries by independent investigators.

In summary, studies utilizing either the patch testing technique or immersion/ROAT techniques have not identified a NOEL for hexavalent chromium, although a level of 1 ppm would certainly approach a NOEL. Based upon one study of solid-phase exposure (Nethercott et al., 1994), a NOEL was not observed; however, a minimal elicitation threshold of 0.089 $\mu\text{g Cr(VI)}/\text{cm}^2$ for 10% of Cr(VI)-allergic individuals has been proposed. In another study (Wass and Wahlberg, 1991), a NOEL for solid-phase exposure (utilizing synthetic sweat to assess extraction) of 0.03 $\mu\text{g Cr(VI)}/\text{cm}^2$ of skin was found, while a minimal elicitation threshold of 0.04 $\mu\text{g Cr(VI)}/\text{cm}^2$ of skin was noted in 1/5 (20%) of the volunteers studied. However, these values for solid-phase contact with hexavalent chromium need to be duplicated by other investigators and the confounding effect of pH on solid phase absorption needs to be assessed.

SYSTEMIC ELICITATION OF HEXAVALENT CHROMIUM ACD

Ingestion

As previously mentioned, individuals allergic to hexavalent chromium often continue to have persistent dermatitis despite avoidance of topical exposure to chromium. Although the trigger factor(s) for persistent disease is (are) not clearly known, oral consumption of chromium is thought to play a role.

In the United States, the daily dietary intake of chromium has been estimated at between 5 and 100 μg per day, with the mean being 50–60 μg (Kumpulainen et al., 1979; Anderson and Kozlovsky, 1985). Several studies have reported flares of dermatitis in chromium allergic patients after ingesting 50 μg potassium dichromate (17.5 μg chromium). Fregert (1965) challenged 5 chromium-allergic patients with a 50- μg oral dose of potassium dichromate; all 5 reacted within 2 h with a blistering

TABLE 5
Human Cr(VI) concentration-effect data reported in the medical literature

Mean concentration of Cr(VI) (ppm)	Circumstances of exposure	Effect	Reference
4.3	Exposure to detergent*	Apparent induction and elicitation of Cr(VI) ACD	Quinones and Garcia-Munoz (1965)
5 ^a	ROAT	ACD in 20% of chrome-sensitive subjects	Basketter et al. (2001)
5.2	Exposure to detergent ^b	Apparent induction and elicitation of Cr(VI) ACD	Feuerman (1971)
8.9	Patch test with Cr(VI) solution	ACD in 14% of chrome-sensitive subjects	Allenby and Goodwin (1983)
10	Patch test with Cr(VI) solution	Dermatitis evidenced by increased cutaneous blood flow	Eun and Marks (1990)
10	Patch test with Cr(VI) solution	ACD in 17.6% of chrome-sensitive subjects	Basketter et al. (2001)
10	Immersion of finger in Cr(VI) solution for 10 min/day for 1 week	ACD in 100% of chromium-sensitive subjects	Neilsen (2000)
10 to 20	Cement workers ^b	Induction and elicitation of Cr(VI) ACD	Burrows (1983)
10 (pH 11.7)	Patch test study	Elicitation of ACD in 10% of chromium-sensitive subjects	Zelger (1964)
15	Analysis of published patch test data	Elicitation of ACD in 10% of chromium-sensitive subjects	Stern et al. (1993)
20	Drinking water	Oral ulcers	Zhang (1987)
20	Application of Cr(VI) solution to superficial scratch on skin	Chrome ulcer	Walsh (1953)
25	Immersion of forearm for 30 min in Cr (VI) solution	Dermatitis in 38% of chrome-sensitized subjects	Fowler et al. (1999)
440	Reinterpretation of Kosann et al. (1998) patch test data	Calculated minimum Cr(VI) concentration necessary to elicit ACD in 10% of sensitized people	Finley et al. (2000)

^aMixed with 1% sodium lauryl sulfate.

^bThese products may or may not have been diluted with water prior to use. The reported concentration of Cr(VI) is believed to be that of the dry powder.

dermatitis of the hands, and 1 of the 5 evolved into a generalized dermatitis. In a placebo-controlled study, Sertoli et al. (1985) similarly challenged 3 chromium-allergic patients with 50 μ g potassium dichromate and noted a flare of the dermatitis in 1 of the 3. Finally, in a larger study, Rudzki and Prystupa (1994) evaluated 30 chromium-allergic individuals: 13 of the 30 reacted to an oral dose of 7.1 mg potassium dichromate (2.5 mg chromium) and 1 of 30 reacted to 0.142 mg potassium dichromate (50 μ g chromium).

In a double-blind, placebo-controlled study utilizing 2.5 mg chromium as potassium dichromate, Veien et al. (1994) found that 17 of 30 chromium-allergic patients reacted to oral ingestion of chromium, but not to placebo. Two of their 30 patients reacted to both placebo and chromium, 4 of the 30 reacted only to placebo, and 7 of the 30 did not react to either chromium or placebo. Of these 30 volunteers, 23 had a blistering type of rash on the hands referred to as dyshidrosis, a condition that some authors feel is partly produced by oral ingestion of known contact

dermatitis allergens. Among the 23 patients with dyshidrosis in the Veien et al. (1994) study, 16 (70%) reacted to chromium ingestion. Furthermore, it would appear that such flares of dermatitis occur not only with ingestion of hexavalent chromium, but also naturally occurring trivalent chromium. Fowler (2000) recently reported the case of a 35-year-old chromium allergic male whose generalized dermatitis was the result of ingestion of unknown amounts of chromium picolinate as a dietary supplement.

For protection against ACD resulting from ingestion of hexavalent chromium, a NOEL cannot be calculated, as adequate dose/response studies are not available. Stern et al. (1993), in their analysis of the Fregert (1965) data, calculated a lowest-observed-effect level (LOEL) for elicitation of chromium-allergic dermatitis in sensitized individuals following a single acute oral dose of 0.26 $\mu\text{g/kg}$.

Inhalation

The ability of inhaled chromium to induce dermatitis in chromium allergic patients is less well documented. Shelley (1964) reported the case of a 40-year-old crane operator who had a 14-year history of an intermittent hand dermatitis that was induced by chromium sensitization when he worked with linoleum paste containing hexavalent chromium. Shelley's patient developed the explosive onset of a dyshidrotic (hand) eczema following exposure to acetylene welding fumes. Since welding rods can contain up to 32% chromium, and since airborne, primarily facial, reactions to chromium have been reported in arc welders (Fregert and Ovrup, 1963), Shelley assumed his patient's dyshidrotic flare was due to chromium absorbed systemically via inhalation.

Perhaps the most well-documented case of the effects of inhaled chromium on allergic individuals is that of De Raeve et al. (1998), who studied a 48-year-old cement floorer with a long-standing history of known hexavalent chromium allergy. This individual also had complaints of increasing episodes of asthma, which he related to the work environment. A bronchial provocation test with 0.01% potassium dichromate (35 ppm chromium) for 31 minutes resulted in an "early/late" bronchial reaction, with a decrease in forced expiratory volume in 1 s (FEV1) of 29%. Repeat bronchial provocation testing with dried cement (containing 12 ppm hexavalent chromium) was equivocal, with a 13% decrease in FEV1. Air analysis performed at the work site of this floorer revealed ambient concentrations of 0.6 $\mu\text{g}/\text{m}^3$ of total chromium. The authors hypothesized that such low levels of chromium were unlikely to be responsible for his asthma. They speculated that it was more likely that this heavy smoker contaminated his cigarettes with hexavalent chromium, thus accounting for inhaled levels of chromium greater than the ambient air analysis would indicate. Whether, in addition to asthma-like symptoms, this worker's dermatitis flared following inhalation of hexavalent chromium is not clear. However, it is mentioned that he complained of itching during the inhalation challenges.

No data are available for calculating a NOEL or LOEL for allergic contact dermatitis reactions following inhalation of hexavalent chromium.

SUMMARY

Based upon the data from cement workers, at least 4–5% of persons chronically exposed to Cr(VI) at concentrations less than 10–20 ppm will become sensitized. Elicitation of chromium ACD occurs in a significant number of chromium sensitive subjects exposed to 10–25 ppm Cr(VI).

Chromium skin ulcers have occurred following exposures in the range of 20–25 ppm Cr(VI). Chromium skin ulcers are a manifestation of chromium dermal toxicity and are a separate reaction from chromium ACD. All persons exposed to chromium at these concentrations are potentially at risk for development of chromium irritation and skin ulcers. The lowest concentration of Cr(VI) necessary to produce an ulcer is not known. However, based upon the available data, it is highly probable that exposure levels that protect against the induction and elicitation of ACD to hexavalent chromium will be sufficient to protect against its cutaneous irritant effects.

Regarding chromium in a solid phase, the data from Wass and Wahlberg (1991) would suggest that levels $<0.03 \mu\text{g}/\text{cm}^2$ skin (as assessed by extraction using synthetic sweat) might represent a NOEL; however, the effect of pH on solid-phase reactivity has not been studied.

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