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Skin Permeation and Cutaneous Hypersensitivity As a Basis for Making Risk Assessments of Chromium As a Soil Contaminant

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A literature review of experimental and human exposure studies of skin permeation and cutaneous hypersensitivity reactions evoked by chromium was carried out to provide a basis for making a risk assessment of chromium as a soil contaminant. *In vitro* and *in vivo* studies demonstrated that 1 to 4% of the applied dose of hexavalent and trivalent chromium to guinea pig skin penetrated skin within 5 to 24 hr after application. Ultrastructural investigations showed that hexavalent chromium localized intracellularly and extracellularly in the upper layers of guinea pig epidermis. Only minute quantities of hexavalent chromium are required to elicit a positive hypersensitivity reaction in susceptible individuals; using a patch dose of 20 µg, only 2 µg were required to evoke a positive skin reaction in hypersensitive subjects. The potential of hexavalent chromium to produce a skin sensitization reaction is readily demonstrated using animal models. The incidence and characteristics of chromium-induced skin hypersensitivity as a clinical entity are described. A health effects survey of populations exposed to chromium slag in soil in Tokyo, Japan extending over 8 years indicated a tendency toward symptoms characterized as headache, chronic fatigue, and gastrointestinal complaints, positive occult blood tests, minute hematuria and albuminuria suggestive of incipient renal disease, and a tendency toward an increase in contact dermatitis that was seasonally related. Multicenter patch test titration studies in human subjects using an incidence of positive patch tests of 10% or less showed that the threshold for skin hypersensitivity reactions to hexavalent chromium was determined to be of the order 0.001%, equivalent to 10 ppm or 10 mg/kg or 10 mg/L. Analysis of soil samples was conducted to predict the hexavalent chromium level from the total chromium level. Based on these data, the cleanup level of total chromium in soil is designated as 75 mg/kg. It is proposed that levels of total chromium lower than 75 mg/kg in soil would avoid undue risk of contact dermatitis.

Introduction

The potent skin allergenicity of chromium has been well documented in the literature, and chromium compounds have been reported to be the most frequent sensitizing agent in man (*1–3*). Most of the occurrences of contact dermatitis cited are the result of occupational exposures. Consequently, the greatest frequency of chromium-induced cutaneous hypersensitivity has been reported to occur in men of working age, i.e., ages 21 to 70 (*4*). Workers in the building trades are especially prone to chromium-induced skin hypersensitivity reactions due to the presence of chromium compounds in cement and other building materials. The early history of chromium-related dermatitis, occupational activities, and industrial compounds associated with chromium-induced dermatitis and clinical characteristics of chromium-related allergic contact dermatitis have been reviewed (*5*). Geographically, the prevalence of susceptibility to chromium-induced contact dermatitis is widespread. For example, the North American Contact Dermatitis Group was formed in 1970 to provide a rational basis for selected antigens for patch test screening of subjects exhibiting contact dermatitis lesions. As part of this program, 0.5% potassium dichromate in petrolatum was applied under a 10-mm

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diameter occlusive patch for 48 hr to 1200 subjects located in 10 centers in North America (*6*). Positive test reactions at the various sites ranged from 2 to 20%, with an overall reactivity rate of 8%; in New York, the positive patch test rate was 9% (Table 1).

The presence of chromite ore processing waste used as landfill at sites in residential, commercial, and industrial areas in Hudson County, New Jersey, represents an uncommon circumstance with the potential for the occurrence of significant adverse health effects. In contrast to occupational exposures involving a select group of subjects for a defined interval during the work week and with the probability that industrial hygiene and occupational safety measures have been instituted, the exposure of the general population comprising all age groups, including children and the elderly, with an undefined incidence of underlying diseases, varying nutritional status, and long-term, continuous contact without protective measures presents a particularly difficult obstacle to arriving at an appropriate risk assessment of chromium under these conditions. The U.S. Environmental Protection Agency considers hexavalent chromium to be a known human carcinogen by inhalation exposure and also states that contact dermatitis is likely to be associated with low-level hexavalent chromium exposure (*7*). However, in contrast to the induction of cancer, contact dermatitis may require only a relatively short-term, superficial exposure.

This report presents the results of a review of the literature of skin permeation and cutaneous hypersensitivity reactions evoked by chromium derived from both laboratory experimental investigations and also from studies of human exposure. The primary objective of this survey was to collate and evaluate these data to provide a basis for making a risk assessment of chromium as a soil contaminant. A secondary objective of this review and evaluation was to delineate possible areas for additional research.

Table 1. Positive skin patch test rate to 0.5% potassium dichromate in petrolatum at 10 centers in North America, 1972.

Center	No. of subjects	Positive patch test rate
Bangor, Maine	59	10
Detroit, Michigan	20	20
Hanover, New Hampshire	197	9
New Orleans, Louisiana	24	12
New York, New York	44	9
Portland, Oregon	229	10
Richmond, Virginia	207	4
San Francisco, California	126	9
Vancouver, British Columbia	165	8
Total	1200	8
Overall positive patch rate		8

Results

Skin Permeation

To gain an understanding of the mechanisms involved in transdermal penetration, skin as a diffusional barrier can be represented as a multilayer model (Fig. 1). The stratum corneum is the principal barrier to permeation. The stratum corneum is nonviable and physiologically inactive; diffusion through this layer is a passive process. The viable epidermis can carry out bioconversion. Although epidermal metabolic activity is only a fraction of that found in the liver, the large surface area of skin and its proximity to the environment classifies it as a metabolizing organ of significance.

The epidermal-metabolizing activity has relevance to chromium based on a proposed working hypothesis for skin penetration and pathogenesis of contact sensitivity (*1*). It has been postulated that hexavalent chromium penetrates cells and intracellular organelles relatively easily and is converted to trivalent chromium intracellularly. The trivalent chromium generated within epi-

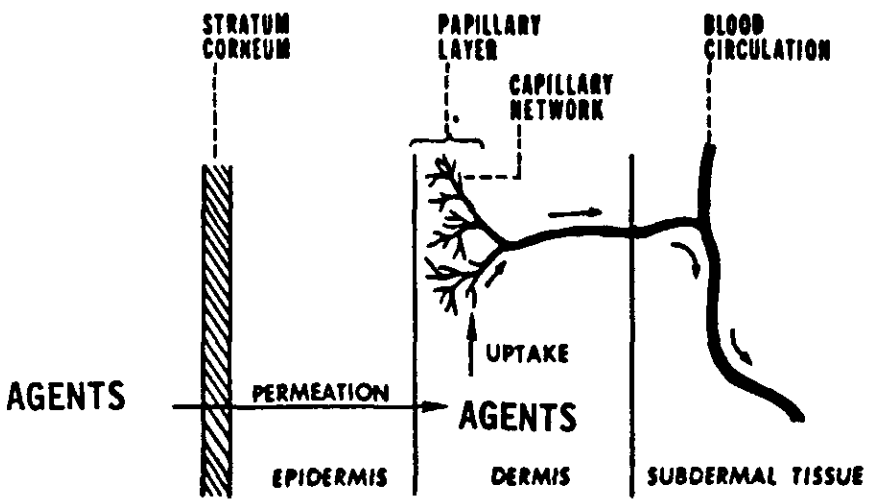

FIGURE 1. A multilayer skin model showing the sequence of transdermal permeation of agents: sorption by stratum corneum, permeation across viable epidermis, and uptake by the capillary network in the dermal papillary layer for system distribution. Adapted from Chien (*8*).

dermal cells reacts with antigenic proteins to evoke the release of the cascade of inflammatory mediators, which results in expression of contact hypersensitivity.

In contrast, trivalent chromium has been postulated to penetrate cells relatively poorly and to bind to nonspecific proteins. This may explain the lesser skin hypersensitivity potency of trivalent chromium compared to hexavalent chromium. The epidermis may also bind chromium to form a depot. The dermis provides a vehicle for chromium uptake into the systemic circulation via the capillary network in the dermal papillary layer. The dermis may also serve as a reservoir for chromium by binding it to the collagen matrix.

The methodology employed in the *in vitro* and *in vivo* skin permeation studies has been comprehensively reviewed (*8–11*). One standard *in vivo* procedure involved applying a weighed amount of the agent in a container or patch to the skin, followed by determination of the remaining agent at the application site after different time intervals. This procedure is variously referred to as analysis by difference, remainder analysis, or residual patch assay. The technique was extended to determination of skin penetration of gamma-ray-emitting ^{51}Cr to guinea pigs *in vivo* by means of a scintillation counter and collimator (*12*). Results are expressed in terms of a calculated disappearance constant and also as the disappearance percentage of the applied dose from the application site over a 5-hr interval. This procedure may underestimate skin penetration because chromium present in the skin in a depot would be detectable by the scintillation counter and would be calculated as part of residual agent at the skin surface.

The remainder analysis technique was used to determine skin penetration of hexavalent and trivalent chromium in guinea pigs *in vivo* (*13*). Skin penetration was concentration dependent for both compounds. Maximal skin penetration for hexavalent chromium amounted to 4% of the applied dose/5 hr at 0.261 M (Fig. 2). For trivalent chromium, this was observed at 0.017 M (equivalent to 0.5%, the standard patch test concentration) and amounted to 2.2%/5 hr (Fig. 3). At 0.261 M, the skin permeation rate of hexavalent chromium was 690 $\mu M/cm^2/hr$, 2-fold higher than trivalent chromium, which was 330 $\mu M/cm^2/hr$ (Fig 4.) Additional studies with hexavalent chromium as sodium chromate in guinea pigs *in vivo* indicated that skin penetration was higher with increasing alkaline pH (6.5–12.8) compared to chromium solutions of pH 5.6 and lower (5.6–1.4) (*14*).

Another *in vivo* experiment was conducted wherein ^{51}Cr hexavalent chromium as sodium chromate was applied to the skin of guinea pigs, and skin permeation was determined by assay of the ^{51}Cr content present in excreta and organs after 24 hr (*15*). In guinea pigs, skin penetration of chromium amounted to 1.30% of the applied dose after 24 hr, and this was increased about 9-fold to 12.50% of the applied dose/24 hr by pretreating the skin with alkali (Table 2).

Ultrastructural investigations have also been carried out to determine the distribution of chromium in the

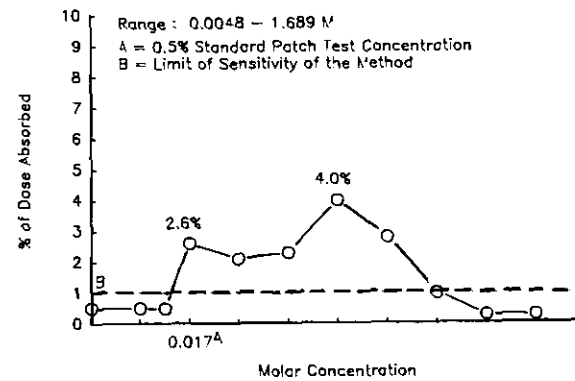

FIGURE 2. Skin permeation of sodium chromate in guinea pigs *in vivo*: disappearance of dermal dose ^{51}Cr (*13*).

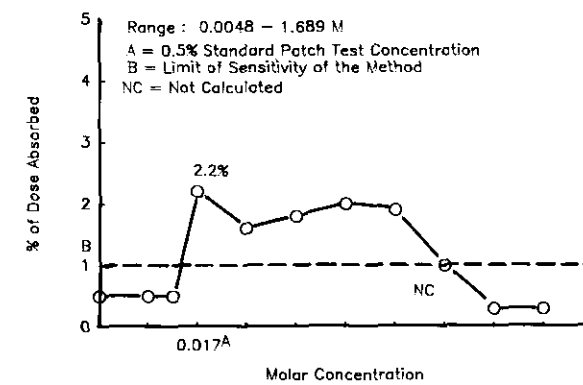

FIGURE 3. Skin permeation of chromic chloride in guinea pigs *in vivo*: disappearance of dermal dose ^{51}Cr (*13*).

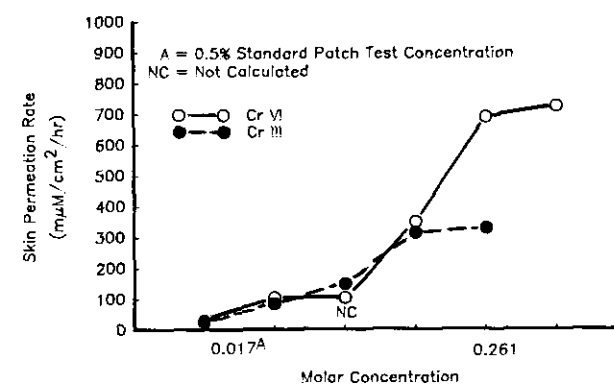

FIGURE 4. Skin permeation rate of sodium chromate and chromic chloride in guinea pigs *in vivo* (*13*).

epidermis of nonsensitized and sensitized guinea pigs (*16*). In both groups, chromium rapidly penetrated the skin and was found localized intracellularly and in the extracellular space in the upper epidermal layers, including the horny, granular, and upper spinous layers. However, the basal and suprabasal cells showed only extracellular and plasma membrane localization with-

Table 2. Skin absorption of chromium in guinea pigs using percent of dose in organs and excreta as end points (*15*).

Group	% Applied dose/24 hr		
	Organs[a]	Excreta	Total
Chromate (no pretreatment)	0.19	1.11	1.30
Chromate + sodium hydroxide (pretreatment)[b]	2.48	9.97	12.50

[a]Heart, liver, spleen, kidneys, lung.
[b]0.5 N NaOH, three times daily for 1 week.

out intracellular penetration of chromium. The Langerhans cells showed activation characterized by increased number of organelles, endocytic formation, and Berbeck granules, but intracellular localization of chromium was not discernible. This characteristic intraepidermal distribution my be related to the intracellular conversion of hexavalent chromium to the immunogenic trivalent form. In addition, these results also suggest that intracellular localization of chromium into activated Langerhans cells is not required for effective presentation of the hapten to T-cells.

Skin penetration of chromium can also be enhanced by administration via iontophoresis. In guinea pigs, iontophoresis increased skin permeation of chromium over 7-fold during the first hour and over 3-fold during 1 to 5 hr of administration compared to epicutaneous administration (*17*).

Quantitation of the Hypersensitivity Reaction

Only minute quantities of chromium are required to penetrate skin to elicit a positive hypersensitivity reaction in susceptible individuals. Using a patch dose of 20 µg of sodium chromate, only 2 µg was required to evoke a positive skin reaction in hypersensitive subjects (*18*). There was little difference in amount of skin permeation of chromium in normal individuals at patch removal after 48 hr of application. After 1 month, the amount of chromium in skin of normal individuals was markedly depleted and was even less in hypersensitive individuals (Table 3). This latter finding may be explained by the shedding of stratum corneum and superficial epidermal cells as a result of the inflammatory skin reaction at the patch test site. Thus, based on both experimental and human exposure studies, the very small amounts of chromium required to invoke a hypersensitivity reaction can be readily attained in skin.

Immunologic Mechanisms of Chromium Contact Dermatitis

Chromium contact dermatitis is a delayed hypersensitivity reaction classified as a type IV cell-mediated immune response. The development of chromium contact dermatitis has been described as occurring in four phases (*1*). In phase I, the refractory phase, skin

Table 3. Quantitative aspects of hexavalent chromium sensitization.

Subjects	Concentration at skin application site, µg	
	At patch removal[a]	After 1 month
Normal		
A	1.6	0.22
B	1.6	0.13
Hypersensitive		
C	1.8[b]	0.02
D	2.1[b]	None

[a]Patch dose of sodium chromate 20.8 µg, applied for 48 hr.
[b]Positive skin reaction characterized by erythema, infiltration, and papulae (*18*).

inflammation does not occur, but the chromium hapten penetrates the skin and conjugates with specific epidermal proteins. In phase II, the induction phase, the hapten conjugate interacts with T-lymphocytes. In lymph nodes, T-lymphocytes are transformed into immunoblasts and divide into memory and effector cells. In phase III, the elicitation phase, a secondary chromium challenge activates the effector cells, releasing the cascade of mediators that cause inflammation of the skin. In phase IV, the persistence phase, effector lymphocytes continue to recognize the chromium-hapten conjugate, and the inflammatory reaction in skin continues.

Animal Models of Chromium-Induced Delayed-Type Hypersensitivity

Classically, guinea pig sensitization tests have been used to assess the potential of agents to evoke skin sensitization reactions in human subjects. All of these guinea pig tests involve induction procedures using the test agent followed by a rest interval and then a subsequent challenge with the test agent. The various types of guinea pig sensitization tests including the Draize, open epicutaneous, Buehler, Freund's complete adjuvant, optimization, split adjuvant, and maximization tests have been reviewed (*19*). Hexavalent chromium has been shown to be a potent skin sensitizer in guinea pig tests (*20,21*). The propensity for chromium to elicit skin sensitization in guinea pigs is a probable explanation for selection of this species for skin permeation studies to obtain correlative data.

More recently, an alternative sensitization test, the mouse ear swelling test (MEST) has been developed (*22*). In addition, a method for the calculation and classification of relative potencies of dermal sensitizers in animal and human test systems has been proposed (*23*) and is shown in Table 4. Using this approach, the sensitization potential of potassium chromate was compared with *p*-phenylene diamine in the MEST, guinea pig maximization, and guinea pig closed patch tests and also with the results of patch tests in human subjects (*24*). These results are shown in Table 5. Based on this comparison, it was stated: "Potency estimates on potassium

Table 4. Potency indices and corresponding hypersensitivity potential rankings.

Class	Potency index	Ranking of skin hypersensitivity potential
I	> 4.0	Severe
II	4.0 > 3.0	Strong
III	3.0 > 2.0	Moderate
IV	2.0 > 1.0	Mild
V	1.0 > 0.0	Weak or questionable

Table 5. Comparative sensitization potential of potassium dichromate and *p*-phenylene diamine in animal and human test systems.

	MEST[a]		% Sensitized		
Agent	% Sensitized	% Swelling	GPMT[b]	Guinea pig closed patch	Human
p-Phenylene diamine	67	109	100	100	53
Potassium dichromate	40	114	75	15	(II)[c]

[a]MEST, mouse ear swelling test.
[b]GPMT, guinea pig maximization test.
[c](II), strong sensitizer (*23*).

dichromate as a sensitizer indicate it to be similar to *p*-phenylene diamine and hexamethyldiisocynate as a sensitizer" (*24*).

Chromium-Induced Skin Hypersensitivity As a Clinical Entity

Allergic contact dermatitis from chromium as a distinct clinical entity that arises from numerous types of occupational exposure has been extensively reviewed (*1,2,5,25,26*). It is important to recognize that there is no relationship between the classic chromium ulcer lesion that occurs in skin and mucous membranes and allergic sensitization of skin.

Beginning in 1925, occupationally related allergic hypersensitivity associated with positive patch tests was reported in the literature. In 1950, the report on chromium as the causative agent in cement dermatitis further focused attention on chromium-induced cutaneous hypersensitivity reactions (*27*). The early history of chromium-related dermatitis has been reviewed by Adams (*5*).

Chromium-induced allergic contact dermatitis is characterized as generally eczematous in appearance, with the time required for clinical manifestation following exposure to be variable, sometimes occurring years after initial contact. The lesions are chronic or sometimes diminish followed by recurrent relapse. Most of the lesions occur in the fingers and finger webs, front of wrists, and the backs of hands, but some reports state that lesions occur at other sites. The pattern of lesions is highly variable and has been variously described as resembling nummular, seborrheic, stasis, or atopic dermatitis. Other reports cite the resemblance of chromium dermatitis to ragweed dermatitis.

There are several reports indicating that exposure to sunlight or short wavelength ultraviolet light exacerbates the severity of chromium dermatitis, and other studies indicate that the incidence is seasonal, most often occurring between April and mid-November, with the peak occurring in September (*1,2,5*). Some case reports emphasize the occurrence of severe pruritis either before or concomitant with frank skin lesions (*26*). The preponderance of chromium dermatitis in males most probably reflects a greater occupational exposure. A clear-cut dose-response relationship has not been established; lower concentrations of chromium have caused a greater incidence of hypersensitivity reactions than observed at higher concentrations.

The health effects of chromium dermatitis are significant. The lesions have been reported to persist for several years in many subjects and significant work time loss has occurred. The chronicity of chromium dermatitis together with the unavailability of specific treatment is the basis of the relatively poor prognosis generally given. Maintenance of chromium levels as low as possible in the environment is emphasized, but this strategy is more feasible in the workplace than in settings involving exposure to the general population.

Health Effects Survey of Populations Exposed to Chromium Slag in Soil Tokyo, Japan

Whereas there are extensive data available on the health effects of chromium compounds as a result of occupational exposure, only limited information is available concerning the health status following environmental exposure of general populations. In this context, the longitudinal health effects survey being conducted by the Tokyo Metropolitan Government Bureau of Sanitation (*28*) is noteworthy.

In 1973, contamination from chromium slag was discovered at a construction site of the Tokyo subway system. The site was formerly owned by a chemical industry company. Based on these findings, a long-term health survey project was initiated, comparing subjects in contaminated areas with individuals in noncontaminated (control) areas. The health effects survey has currently completed 8 years and is continuing; interim reports have been issued for surveys conducted for the years 1978–1979, 1980–1981, 1982–1983, and 1984–1985.

The survey has used three contaminated block areas and two control block areas in the Tokyo district. The subjects are housewives; a total of 259 subjects in the contaminated areas and 177 subjects in the control areas were evaluated. The evaluation consisted of: *a*) an interview form and questionnaire (Okayama University Medical Interview Form) to delineate signs and symptoms as reported by the subjects; *b*) an in-depth medical examination including clinical interview, physical examination, otolaryngological and dermatological exami-

nations, clinical chemistries, blood chromium levels, urinalysis, and pulmonary function tests.

In the fourth report, covering the years 1984–1985 (*28*), subjects in the contaminated areas reported a tendency toward a higher incidence of complaints characterized as headache, heaviness in the head, chronic fatigue, dizziness, diarrhea, and constipation compared to the control subjects. There also was a trend toward an increase in positive occult blood tests, minute hematuria, and albuminuria in subjects located in the contaminated areas. Further analysis using a positive (++) occult test or over and RBC in the urine of 20 to 25 or more provided the abnormality rates shown in Table 6.

These results suggest that there is a trend toward incipient kidney disease that may become manifest as the epidemiologic survey is continued. Toward this end, the committee directing this survey of health effects from chromium contamination plans to include sulfosalicylic acid qualitative tests for low molecular weight urinary protein in the renal function test panel in further examinations.

The results of the dermatological examinations indicated an increase in abnormalities of the skin in subjects in the contaminated areas during the summer months but not during the winter months. Overall, there was an increase in contact dermatitis and eczema of the hands in the contaminated areas compared to the controls. This seasonal trend is noteworthy in view of reports indicating that exposure to sunlight or short wavelength ultraviolet light exacerbates the severity of chromium dermatitis as previously cited (*1,5*). The committee directing this health effects survey also plans to follow up these observations of dermatologic abnormalities in the chromium-exposed population.

Threshold Concentration Required for Positive Hexavalent and Trivalent Chromium Patch Tests

One approach to assessing the susceptibility of populations to chromium-induced dermatitis is to use the patch test titration technique. In this procedure, the test population, almost invariably hypersensitive subjects to contact dermatitis, are patch tested using successively decreasing concentrations of hexavalent or trivalent chromium to determine the threshold concentration for evoking a positive skin reaction.

Table 6. Abnormality rates.

Area	Incidence of positive occult blood tests[a] and hematuria,[b] %
Contaminated area no. 1	8.4
Contaminated area no. 2	10.2
Contaminated area no. 3	10.6
Control area no. 1	4.7
Control area no. 2	2.1

[a]Occult blood test = ++ or over.
[b]Hematuria = 20 to 25 RBC or more in the urine.

Several investigators have provided summary tabulations of a series of patch titration tests. Table 7 represents a tabulation of patch titration tests of hexavalent chromium compounds. Patch titration studies of dichromate at concentrations ranging from 0.5 to 0.001% are shown in Table 8. In a similar patch test titration study, 14 subjects were challenged with dichromate at concentrations ranging from 0.5 to 0.00025% (*35*). These results are shown in Table 9. In a direct comparison in 50 chromium-sensitive subjects, chromate evoked a positive patch test rate in 8% of the subjects at 0.001% compared to 4% with 0.01% dichromate (*34*).

Thus, in several multicenter studies involving 301 challenge tests in human subjects and employing an incidence of positive patch tests of 10% or less, the threshold concentration for skin hypersensitivity reactions to hexavalent chromium was determined to be of the order of 0.001%, equivalent to 10 ppm, 10 mg/kg or 10 mg/L.

Skin hypersensitivity data for trivalent compounds in human subjects are limited; moreover, the sensitization potency varies with the trivalent chromium salt tested. Table 10 contains the results of representative patch titration studies of the sulfate, nitrate, and chloride salts of trivalent chromium. While there are fewer patch titration studies available for trivalent chromium as compared to hexavalent chromium, and the sensitization potency varies with the salt tested, it is feasible to designate at least a provisional threshold concentration for skin sensitization evoked by trivalent chromium compounds.

Using the data obtained with the sulfate and nitrate salts and employing an incidence of 10% or less, an approximate threshold concentration for evoking skin hypersensitivity by trivalent chromium compounds is of the order of 0.05% or 500 ppm or 500 mg/kg. This threshold level is 50-fold higher than that determined for hexavalent chromium compounds.

Table 7. Patch titration studies of hexavalent chromium compounds in human subjects.[a]

Hexavalent chromium compound	Concentration of hexavalent chromium compound	Total no. of subjects challenged	No. of positive subjects	% of total subjects
Potassium chromate	0.05	33	11	33
	0.02		10	30
	0.005		9	27
	0.001		3	9
Chromic acid	0.05	13	5	39
	0.01		2	15
	0.005		5	39
	0.001		1	8
Potassium dichromate	0.1	13	14	42
	0.05		17	52
	0.01		2	6

[a]Modified from Haines and Niebor (*1*).

Table 8. Patch titration studies of dichromate in human subjects (*29*).

Reference		Dichromate concentration, %						Total *n*
		0.5	0.2	0.1	0.005	0.01	0.001	
(*30*)	*n*			2	8	5		15
	%[a]			13	53	13		
(*31*)	*n*	10		7		5	2	24
	%	42		29		21	8	
(*32*)	*n*	49		35		13		97
	%	51		36		13		
(*33*)	*n*	1	4	25		4	1	35
	%	3	11	71		11	3	
(*34*)	*n*			23	25	2		50
	%			46	50	4		
Total	*n*	60	4	92	33	29	3	221
	%[b]	27	2	42	15	13	1	

[a]Percent of subjects with positive skin reaction of total number of subjects tested within each study.
[b]Cumulative percent of subjects with positive skin reaction of total number of subjects tested at each concentration in the studies.

Table 9. Patch titration studies of dichromate in human subjects (*35*).

Dichromate concentration, %	*n*	Percent
0.5	14	100
0.25	10	71
0.025	3	21
0.0025	2	14
0.00025	1	7
Total no. of subjects	14	

Table 10. Patch titration studies of trivalent chromium salts in human subjects.

Trivalent chromium salt	Total no. of subjects	Concentration	No. of positive subjects	Percent	Reference
Sulfate	28	0.50%	12	43	(*1*)
		0.10%	7	25	
		0.05%	3	11	
		Negative[a]	6	21	
Nitrate	28	0.50%	5	18	(*1*)
		0.10%	2	7	
		0.05%	3	11	
		Negative	18	64	
Chloride	17	0.50 M		11	(*36*)
	22	0.07 M		22	

[a]Negative indicates no reaction or no response.

Derivation of a Risk-Based Chromium Level in Soil Contaminated with Chromite Ore Processing Residue

Contact dermatitis is one of the few health end points, other than respiratory cancer, that is likely to be associated with low-level hexavalent chromium exposure. Based on epidemiologic surveys using the positive patch test rate to hexavalent chromium as an index (Tables 7 and 8), allergic contact dermatitis is a common acute effect resulting from exposure of the skin to low levels of chromium. From a review of these surveys it has been determined that at concentrations of hexavalent chromium in solution of less than 0.001% (10 mg/L), the incidence of contact dermatitis will be reduced to less than 10% in chromium-sensitive subjects. A source of uncertainty in using these data for a risk assessment for soil is the comparison of parts per million in solution to parts per million in soil. For a number of reasons it was concluded that an assumption of equivalence was the most appropriate. The 10 mg/L of hexavalent chromium in the solution used for a patch test would have the same potential for eliciting a response as 10 mg/kg (10 ppm) hexavalent chromium in soil. Preliminary unpublished data from the New Jersey Department of Environmental Protection have shown more hexavalent chromium extracted from the chromite ore processing residue by a neutral extraction than by the alkaline digestion method used for the analysis of hexavalent chromium in waste (*41*). Therefore, a volume of sweat (approximately the same composition as the neutral extraction medium) equal to a volume of processing residue on skin should lead to at least the same concentration in solution as was contained in the soil. It is also apparent that as the sweat evaporates, a higher concentration will be achieved.

Since there is no method of analysis for hexavalent chromium in soil that is currently approved by the U.S. Environmental Protection Agency, it was necessary to use previous analysis of Hudson County, New Jersey, soils to construct a ratio of hexavalent to total chromium at contaminated sites and then express the acceptable soil cleanup levels in terms of total chromium.

The relationship between hexavalent and trivalent chromium is a dynamic one, which is affected by soil type and mineral content, pH, solubility, and other factors (*40*). These factors vary over times and between locations, so that the hexavalent/total chromium relationship that exists in one sample may be different at another time or location.

In order to carry out this risk assessment, soil samples were collected from approximately 40 sites in Hudson County, New Jersey (*41*). Soil total chromium levels were available for 994 samples, while hexavalent chromium levels were available for 345. From these data, statistical analysis were performed by the New Jersey Department of Environmental Protection to enable the prediction of hexavalent chromium level from total chromium measurements. Since only short-term exposure is necessary to elicit a skin reaction, the estimated 95th percentile of the sample distribution of the ratio between hexavalent and total chromium (0.14) is the most reasonable figure to use when calculating a target soil concentration that protects against contact dermatitis. This target level, approximately 75 mg/kg (10 mg/kg/0.14), is the concentration of total chromium

that would not be expected to result in a hexavalent chromium level greater than 10 mg/kg in Hudson County soil containing the process residue (*37*).

Due to the fact that the cleanup level is based on the potential for developing contact dermatitis, no distinction is necessary between large and small sites or different sites uses.

Discussion

Selection of allergic contact dermatitis as a significant toxic end point to arrive at an appropriate risk assessment of chromium waste as a soil contaminant has a valid basis. Occupationally related contact dermatitis resulting from chromium exposure with resulting work time or the necessity to change occupations to reduce disability has been well documented. However, there is little information available regarding skin sensitivity evoked by long-term exposure to the general population, including children and the elderly. An 8-year follow-up survey in housewives exposed to soil contaminated with chromium slag at a construction site in Tokyo, Japan (*28*) indicated a tendency toward an increase in subjective symptoms such as headache, chronic fatigue, and gastrointestinal effects; a tendency toward an increase in positive occult blood tests in urine, minute hematuria, and albuminuria; and a seasonal increase in the incidence of contact dermatitis during the summer months. These signs and symptoms are further indications of the potential adverse effects of long-term exposure to chromium to general populations.

The seasonal occurrence of increased contact dermatitis is of interest in view of reports indicating that exposure to sunlight or short wavelength ultraviolet light exacerbates the severity of chromium der-matitis. Other factors that add to the complexity of evaluating chromium-induced skin hypersensitivity are the variable patterns of the skin lesions, persistence, lack of reversibility or periodic exacerbations, lack of a strict dose-response relationship, long latency for manifestation of skin lesions in some individuals after exposure, lack of specific treatment other than removal from the contaminated environment, and occurrence of other effects on skin, such as severe pruritis.

It has been amply demonstrated that only minute amounts of hexavalent chromium are required to penetrate skin to elicit delayed contact dermatitis in hypersensitive individuals. For example, using a 20 μg patch of sodium chromate, only 2 μg had to penetrate skin in order to evoke a positive skin reaction in hypersensitive subjects (*18*). *In vitro* and *in vivo* studies carried out in guinea pigs demonstrated that hexavalent chromium can penetrate skin readily, amounting to 1 to 4% of the applied dose within 5 to 24 hr.

Ultrastructural studies using guinea pig skin also showed that hexavalent chromium readily penetrates skin and has a characteristic intraepidermal distribution (*16*). Hexavalent chromium localized both intracellularly and in the extracellular space in the upper epidermal layers, i.e., the stratum corneum, granular, and upper spinous layers. However, hexavalent chromium did not penetrate into the intracellular regions of the suprabasal and basal cells, and distribution in these lower epidermal layers was limited to the extracellular space and at the plasma membrane. This characteristic distribution may be consistent with the proposal that hexavalent chromium is required to penetrate epidermal cells to be converted intracellularly into the trivalent form, which is ultimately involved in eliciting the immunologic response in skin. A diversity of animal models including guinea pigs and mice have conclusively demonstrated that hexavalent chromium is a potent sensitizer of skin under these experimental conditions (*22–24*).

Multicenter patch titration studies have shown that an approximate threshold concentration of hexavalent chromium can be determined that will evoke a skin sensitization reaction in human subjects. In designating a threshold as a criterion, the concentration of hexavalent chromium that evokes a positive skin hypersensitivity patch test reaction in 10% or less of the population was employed; this criterion is equivalent to a lowest observed effect level. Thus, the threshold concentration for skin sensitization of hexavalent chromium compounds was determined to be of the order of 0.001%, and this is a level below which 90% or more of the exposed population will not exhibit a positive reaction. The proposed cleanup level of 75 mg/kg of total chromium should result in an incidence of contact dermatitis that is less than 10% of the exposed general populations.

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REFERENCES

1. Haines, A. T., and Niebor, E. Chromium hypersensitivity. In: Chromium in the Natural and Human Environments. Advances in Environmental Science and Technology, Vol. 20 (J. O. Nriagu and E. Niebor, Eds.), John Wiley and Sons, New York, 1988, pp. 497–532.
2. Burrows, D. Chromium: Metabolism and Toxicity. CRC Press, Inc., Boca Raton, FL, 1983, pp. 137–163.
3. Polak, L. Immunology of chromium. In: Chromium: Metabolism and Toxicity (D. Burrows, Ed.), CRC Press, Inc., Boca Raton, FL, 1989, pp. 51–136.
4. Cronin, E. Contact Dermatitis. Churchill Livingston, New York, 1980.
5. Adams, R. L. Occupational Skin Disease. Grune and Stratton, New York, 1983.
6. North American Contact Dermatitis Group. Epidemiology of contact dermatitis in North America: 1972. Arch. Dermatol. 108: 537–540 (1973).
7. U.S. EPA. Health Assessment Document for Chromium. U.S. Environmental Protection Agency, Research Triangle Park, NC, 1984.
8. Chien, Y. W. Developmental concepts and practice in transdermal therapeutic systems. In: Transdermal Controlled Systemic Medications (Y. W. Chien, Ed.), Marcel Dekker, New York, 1987, pp. 25–81.
9. Tojo, K. Design and calibration of in vitro permeation apparatus. In: Transdermal Controlled Systemic Medications (Y. W. Chien, Ed.), Marcel Dekker, New York, 1987, pp. 127–158.

10. Huang, Y. In vitro evaluations of transdermal drug delivery. In: Transdermal Control Systemic Medications (Y. W. Chien, Ed.), Marcel Dekker, New York, 1987, pp. 159–178.
11. Guy, R. H., Hadgraft, J., Hinz, R. S., Roskos, K. V., and Bucks, D. A. W. *In vivo* evaluation of transdermal drug delivery. In: Transdermal Controlled Systemic Medications (Y. W. Chien, Ed.), Marcel Dekker, New York, 1987. pp. 179–224.
12. Wahlberg J. E. Disappearance measurements, a method for studying percutaneous absorption of isotope-labelled compounds emitting gamma rays. Acta Derm.-Venereol. 45: 397–414 (1965).
13. Wahlberg, J. E., and Skog, E. Percutaneous absorption of trivalent and hexavalent chromium. Arch. Dermatol. 92: 315–318 (1965).
14. Wahlberg, J. E. Percutaneous absorption from chromium (^{51}Cr) solutions of different pH, 1.4–12.8. Dermatologica 137: 17–25 (1968).
15. Czernielewski, A., Brykalski, D., and Depczyk, D. Experimental investigations on penetration of radioactive chromium (^{51}Cr) through the skin. Dermatologica 131: 381–396 (1965).
16. Saloga, J., Knop, J., and Kolde, G. Ultrastructural cytochemical visualization of chromium in the skin of sensitized guinea pigs. Arch. Dermatol. Res. 280: 214–219 (1988).
17. Wahlberg, J. E. Skin clearance of iontophoretically administered chromium (^{51}Cr) and sodium (^{22}Na) ions in the guinea pig. Acta Dermatovener 50: 255–262 (1970).
18. Pedersen, N. B., Fregert, S., Naversten, Y., and Rorsman, H. Patch testing and absorption of chromium. Acta Dermatovener 50: 431–434 (1970).
19. Patrick, E., and Maibach, H. I. Dermatotoxicology. In: Principles and Methods of Toxicology, 2nd ed. (A. W. Hayes, Ed.), Raven Press, New York, 1989, pp. 383–406.
20. Maurer, T., Thomann, P., Weirich, E. G., and Hess, R. Predictive evaluation in animals of the contact allergenic potential of medically important substances. Contact Dermatitis 5: 1–10 (1979).
21. Magnusson, B., and Kligman, A. M. The identification of contact allergens by animal assay. The guinea pig maximization test. J. Invest. Dermatol. 52: 268–276 (1969).
22. Gad, S. C., Dunn, B. J., Dobbs, D. W., Reilly, C., and Walsh, R. D. Development and validation of an alternative dermal sensitization test: the mouse ear selling test (MEST). Toxicol. Appl. Pharmacol. 84: 93–114 (1986).
23. Gad, S. C. A scheme for the prediction and ranking of relative potencies of dermal sensitizers based on data from several systems. J. Appl. Toxicol. 8: 461–467 (1988).
24. Gad. S. C. Acute and chronic chromium toxicity. Sci. Total Environ. 86: 149–157 (1989).
25. Burrows, D. Prognosis in industrial dermatitis. Br. J. Dermatol. 87: 145–148 (1972).
26. Zelger, J. On the pathogenesis and clinical aspects of chromate eczema. Arch. Klin. Expt. Dermatol. 218: 499–542 (1964).
27. Jaeger, H., and Pelloni, F. Test epicutanes and bichromates, positifs dans l'eczema au ciment. Dermatologica 100: 207–216 (1950).
28. Tokyo Metropolitan Government Bureau of Sanitation. Survey of Health Effects from Chromium Contamination: Fourth Report. Tokyo, Japan, March, 1987.
29. Skog, E., and Wahlberg, J. E. Patch testing with potassium dichromate in different vechicles. Arch. Dermatol. 99: 697–700 (1969).
30. Anderson, F. E. Cement and oil dermatitis: the part played by chrome sensitivity. Br. J. Dermatol. 72: 108–117 (1960).
31. Burrows, D., and Calnan, C. D. Cement dermititis: II. Clinical aspects. Trans. St. John Hosp. Derm. Soc. 5: 27–39 (1965).
32. Geiser, J. D., Jeanneret, J. P., and Delacretaz, J. Eczema au ciment et sensibilisation au cobalt. Dermatologica 121: 1–7 (1960).
33. Parila, V. On the role of chrome and other trace elements in cement eczema. Acta Dermatol. 34: 136–143 (1954).
34. Zelger, J., and Wachter, H. On the relationships between chromate and dichromate allergy. A contribution to the analysis of chromium (VI) allergy. Dermatologica 132: 45–50 (1966).
35. Allenby, C. F., and Goodwin, B. F. J. In: Chromium: Metabolism and Toxicity (D. Burrows, Ed.), CRC Press, Inc., Boca Raton, FL, 1983, p. 141.
36. Fregert, S., and Rorsman, H. Allergy to trivalent chromium. Arch. Dermatol. 90: 4–6 (1964).
37. New Jersey Department of Environmental Protection. Derivation of a Risk Based Chromium Cleanup Level in Soil Contaminated with Chromite Ore Processing Residue in Hudson County 1989. CN 409, NJ Department of Protection, Trenton, NJ.
38. Hawley, J. H. Assessment of health risks from exposure to contaminated soil. Risk Anal. 5: 289–302 (1985).
39. Lioy, P., and Daisey, J. M., Eds. Toxic Air Pollution. Lewis Publishers, Chelsea, MI, 1987, pp. 50–51.
40. Bartlett, R. J. Chromium oxidation in soils and water: measurements and mechanisms. In: Proceedings, Chromium Symposium 1986: An Update. Industrial Health Foundation, Pittsburgh, PA, 1986.
41. New Jersey Department of Environmental Protection. Risk Assessment for Chromium Sites in Hudson County, N.J. Prepared by Environmental Science and Engineering, Inc., April, 1989. NJ Department of Environmental Protection, Trenton, NJ.