

ACUTE AND CHRONIC SYSTEMIC CHROMIUM TOXICITY

SHAYNE C. GAD

G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077 (U.S.A.)

ABSTRACT

Although chromium and compounds containing it have been recognized as having potential severe adverse effects on health for more than 160 years, understanding of the systemic toxicology and true hazard of these compounds is still not complete. A review of the current state of knowledge is attempted in this paper, with appropriate attention given to the complications of multiple valence states and solubility.

Selected chromium compounds, particularly hexavalent ones, are carcinogens, corrosives, delayed contact sensitizers, and have the kidney as their primary target organ. But chromium is also an essential element for humans. The body clearly possesses some effective detoxification mechanisms for some degree of exposure to hexavalent chrome compounds. The significant features of acute and chronic chromium toxicity are presented in view of these considerations.

INTRODUCTION

It is not the purpose of this paper to attempt to review and comment on each of the many publications on the subject of chromium toxicology. For those who might wish to so spend their time, I would refer you to one of the three major review documents now available — the Industrial Health Foundations's (IHF) 1980 and 1986 symposium proceedings (IHF, 1981; Serone, 1986) and the Environmental Protection Agency's (EPA) Health Assessment Document for Chromium (EPA, 1984). Rather, in this paper I will attempt to give a synthesis of what we know, and what we don't know, about the systemic toxicity of chromium compounds

Human data has preceded experimental animal data in identifying many of the hazards associated with chromium.

Hexavalent chromium salts have been recognized as occupational health hazards for more than 160 years. As long ago as 1827, Cumin (1827) reported observing cases of skin ulceration and dermatitis in British dye workers who handled potassium dichromate. Later, MacKenzie (1884) reported perforation of the nasal septum in workers exposed to potassium dichromate. The incidence of ulceration or perforation of the nasal septum in workers in industries using chromates during the years before the Second World War was typically very high. The Factory Inspectorate in Great Britain reported in 1930 that of 223 persons examined from the chrome plating industry, 52% had perforated or ulcerated nasal septa (Baetjer, 1950).

During this same period, Parkhurst (1925) reported on the occurrence of delayed contact dermatitis in workers exposed to chromates in the form of pigments on blueprints.

The first reported indication that there was an association between the inhalation of chromates and lung cancer was an epidemiology study performed in Germany and published during the Second World War (Gross and Kosch, 1943). An increased incidence of lung cancer was reported in workers involved in the manufacture of lead pigments. Baetjer (1950) confirmed this finding with a case control study of U.S. chromate workers. It was during this same period that suggestions began to arise that the solubility and valence state of the chromium materials that workers were exposed to were determinants of the degree and nature of the health effects seen in workers.

Prior to the 1950s, the major form of exposure for chromium production workers was in the form of inhalation of acid-soluble, water-insoluble, chromate-chromite mixtures. This process also produced detectable amounts of chromyl chloride gas, which may have been a significant contributor to the carcinogenesis problem in chromium production facilities.

During the late forties and early fifties, the process by which chromium salts were produced was changed and working conditions in these production facilities were significantly improved. The result is now a workplace with much lower total worker exposure levels. Chromyl chloride is no longer found in the plants, and exposure to water-insoluble particles is much reduced.

It is necessary to provide just enough information regarding the chemical forms to set the stage for discussion of what is known, or what we think we know about the biological activity of these materials.

PHYSICOCHEMICAL FACTORS RELATING TO TOXICITY

While chromium compounds can exist in a variety of valence states, those of greatest commercial importance are Cr(II), Cr(III), and Cr(VI). These valence states represent basic, amphoteric, and acidic activities, respectively. Chromium(III) appears to be the most stable and important form. Lower valence forms are readily oxidized and higher valence forms are readily reduced. This factor is of great importance in consideration of environmental releases and long-term contamination, but is not of itself sufficient reason to disregard or minimize the variations in toxicity among valence states where human occupational exposures are involved. Chromium(III), in addition to inorganic salt formation, will form stable organic complexes with proteins, amino acids, and other organic acids. Some of these organic complexes are sufficiently stable that precipitation may not normally occur in the body and thus their biological activity is not entirely mediated through inactivation. Chromium(VI) exists in solution as ionic species which are dependent on pH. At basic and neutral pH, Cr(VI) is largely in the form of chromate. At lower, acidic pHs, the dichromate species becomes the more dominant form and the oxidation potential similarly increases with decreasing pH. Thus, the

TABLE 1

Solubility of selected chromium compounds

Compound	Solubility in water (g/100 ml)
Chromium(III)	
Chromic chloride	Insoluble
Chromic chloride hexahydrate	58.5 at 25°C
Chromic oxide	Insoluble
Chromic sulfate	Insoluble
Chromic sulfate, hydrated (18H ₂ O)	120 at 20°C
Chromium(VI)	
Ammonium dichromate	30.8 at 15°C
Chromium oxide	67.5 at 100°C
Lead chromate	5.8×10^{-6} at 25°C
Potassium chromate	62.9 at 20°C
Potassium dichromate	4.9 at 0°C
	102 at 100°C
Sodium chromate	87.3 at 30°C
Calcium chromate	16.3 at 20°C

oxidation properties of Cr(VI) with respect to organic material, accompanied by a reduction to Cr(III) with stable complex formation, becomes important for an understanding of the biochemical interactions and toxic manifestations of these compounds.

There are also obvious differences in solubility among the more important compounds of chromium, as shown in Table 1. However, there is disagreement in the literature regarding these parameters of solubility, possibly due to reactions of the compounds with other substances, impurities and varying experimental methodologies. These differences in solubility would influence the ease of rate of uptake by the body from an occupational contact.

Particle size would affect both deposition and clearance rates for the "insoluble" or otherwise less soluble compounds. Even for the more soluble compounds, particle size would influence the rate of solution because of surface area to mass relationships, and this in turn may be competitive with clearance rates of particles from the lung.

SYSTEMIC TOXICITY

Much of the research presented here was supported by the IHF Chrome Chemical Committee.

The primary routes of exposure to chromium at hazardous levels are dermal and inhalation, though there are cases of accidents or attempted suicide where significant exposure by the oral route will occur. This overview of systemic toxicity will thus be organized in terms of routes, with some degree of crossover as necessary.

Dermal

Dermal effects are largely related to the acidity and oxidizing potential of the compound or mixture. Irritation or corrosive responses are quite likely with Cr(VI); such effects from contact with Cr(III) are of less probability and severity. While chromium compounds are not likely to be sufficiently absorbed through the intact skin to produce systemic toxicity (kidney damage), if the integument of the skin is significantly disrupted (as in the well-known "chrome burn" process), absorption can occur and acute kidney damage may result as a secondary effect. There is no evidence to suggest that chronic kidney damage may result from dermal contact which does not, of itself, cause a primary effect on the skin. Dermal contact with Cr(VI) compounds can also cause allergic dermatitis or sensitization (Parkhurst, 1925). This effect, however, has not been generally noted for Cr(III) compounds, although persons sensitive to Cr(VI) may also respond to large doses of Cr(III) (Parkhurst, 1925; Fregert and Rorsman, 1964; Gad et al., 1986a). Figure 1 summarizes the available animal and human formal test data on the sensitization potential of potassium dichromate (Gad et al., 1986a). Potency estimates on potassium dichromate as a sensitizer indicate it to be similar to *p*-phenylenediamine and hexamethyl-diisocyanate as a sensitizer (Gad, 1988).

In a study of dermal LD₅₀ values of four chrome salts (Gad et al., 1986b), numerous clinical observations were attributed to all four test compounds and observed in both sexes. Some of the more prevalent observations include: dermal necrosis, eschar formation, dermal corrosion, diarrhea, hypoactivity and dermal edema and erythema. Dermal corrosion was judged to have occurred when skin damage appeared to have been permanent (i.e., observed early in the study and remaining at study termination).

Under the conditions of this test, a single 24-h dermal exposure to any one of the four chromium salts tested is capable of producing acute death. In males, the LD₅₀ ranged from 0.96 g kg⁻¹ for sodium dichromate to 1.86 g kg⁻¹ for potassium dichromate. In females, the LD₅₀ ranged from 1.03 g kg⁻¹ for sodium dichromate to 1.73 g kg⁻¹ for sodium chromate. When using LD₅₀ values, there

TABLE 2

Calculated dermal LD₅₀ values (g kg⁻¹)^a

	Males	Females	Both sexes combined
Sodium chromate	1.33 ± 1.07	1.73 ± 0.28	1.80 ± 0.27
Sodium dichromate	0.96 ± 0.19	1.03 ± 0.15	1.00 ± 0.11
Potassium dichromate	1.15 ± 0.24	1.40 ± 0.24	1.17 ± 0.15
Ammonium dichromate	1.88 ± 0.35	1.34 ± 0.58	1.84 ± 0.18

^aMean ± standard deviation.

MEST										Beuhler (or other closed patch)				
Chemical	Concentrations Utilized(%)					GPMIT					Concentrations Utilized(%)			
	Vehicle	Induction	Challenge	Basis ^a	Vehicle	Intradermal Injection	Topical Induction	Challenge	Vehicle	Induction	Challenge	Vehicle	Induction	Challenge
Potassium Dichromate	25% ETOH	2	2	1	Petrolatum	1	1	0.1	WATER	0.1	0.1(LD)			
p-Phenylene Diamine	70% ETOH	5	10	1	Petrolatum	1	1	1	Ethanol	2	2			

HUMAN PATCH		
Chemical	Concentration Utilized (%)	
	Induction	Challenge
p-Phenylene Diamine	1	1

PRIMARY RESULTS				
Chemical	MEST Results		Closed Patch Results (B)	Human Results (C)
	% Sensitized	% Swelling		
p-Phenylene Diamine	67	109	100	53
Potassium Dichromate	40	114	15	(II)

Fig. 1. Chromate sensitization: Test chemical information.

TABLE 3

Dermal corrosion and irritation potentials (4-h exposure)

	Solid	Solid (moistened with physiological saline)
Sodium chromate	No corrosion/no irritation	No corrosion, but caused well-defined erythema in all six animals, five of which showed edema
Sodium dichromate	No corrosion, but caused well-defined erythema in two of six animals	No corrosion, but caused well-defined erythema in all six animals, five of which showed edema and one of which showed a superficial necrotic focal point
Potassium dichromate	No corrosion/no irritation	No corrosion, but caused well-defined erythema in all six animals, five of which showed edema and three of which showed superficial necrotic focal points
Ammonium dichromate	No corrosion, but caused well-defined erythema in two of six animals	No corrosion, but caused well-defined erythema and edema in all six animals, two of which showed superficial necrotic focal sites

did not appear to be a statistically significant sex difference for any of the four chromium salts (Table 2).

Results from a study of dermal irritation and corrosion due to four chrome salts (Gad et al., 1986b) are summarized in Table 3. In general, all four salts were comparable, with the wetted solids being more irritating than the dry salts, but still not corrosive in a 4-h test. Single animal probes showed that all four salts, if wetted, would be too severe to test in a standard 24-h primary dermal irritation study.

Inhalation

The toxic effects of inhalation exposure to chromium compounds have been extensively studied. The primary danger from inhalation of Cr(VI) compounds is to the respiratory tract as a consequence of their acidic and oxidative nature. Compounds which are soluble in water or serum may be absorbed in the blood and transported to the kidney where, if sufficient Cr(VI) reaches the target organ without having been reduced to Cr(III) by natural body functions, acute damage may result. The essentially insoluble compounds remain in the lung tissue or are transported via mucociliary action to the gut. Absorption from the gut is usually minimal (< 5%) (EPA, 1984) and systemic toxicity normally ensues only if irritation occurs in sufficient degree or reduction to Cr(III) is avoided in either the stomach or the blood. The toxicity of Cr(III) compounds

is generally markedly less (by orders of magnitude) than that of Cr(VI) compounds. It would also be appropriate to note at this point that Cr(III) is an essential element and plays a role in the metabolism of sugars and fats. Chromium deficiency from dietary intake can produce a condition not unlike diabetes.

Certain Cr(VI) compounds, mainly water-insoluble, are recognized as human carcinogens from inhalation exposure (ACGIH, 1985). This association has been confirmed epidemiologically and, in recent animal studies sponsored by the IHF (Steinhoff et al., 1986a,b), has been noted in animals dosed intratracheally. These studies included the particularly interesting finding that the effect was far more severe when a given dose was administered once weekly than when administered in divided doses on a daily basis. Presumably, the tissue irritation produced by the larger amount of material was sufficient to play a role in the induction of cancer. The EPA Science Advisory Board has concluded that there is insufficient evidence to classify Cr(VI) compounds as carcinogens from either oral or dermal exposure. Also, there is no evidence to implicate Cr(III) as a carcinogenic risk from any route of exposure, except where Cr(VI) is shown to be present as an impurity.

In studies of the acute inhalation LC_{50} of four chrome salts, Gad et al. (1986b) found a mean lethal concentration of 104.14 mg m^{-3} for both sexes exposed to sodium chromate. Both males and females were equally susceptible to the effects of sodium chromate. Each of the three remaining chromates was more toxic to the females than to the males. Signs of toxicity elicited by exposure to all four chromates included respiratory distress and irritation and body weight depression. LC_{50} results are summarized in Table 4.

Oral

Oral exposure to chromium compounds generally represents an acute hazard and medical emergency. This emergency requires dealing with (i) burns and corrosion along the oral cavity and upper end of the trachea, and (ii) the acute renal toxicity of absorbed hexavalent chrome compounds. The IHF sponsored testing of the acute oral toxicity of four chrome salts (Gad et al., 1986b) and the results of these tests are summarized in Tables 5 and 6. Of interest and possible significance is the fact that there can be a 50% difference in toxicity depending on concentration used to dose, with the more concentrated materials producing the greatest level of quantitative toxicity for a given dose. This confirms similar findings from the carcinogenic studies.

The primary cause of death to acute chrome exposures (either oral or dermal) is nephrotoxicity, ranging to complete renal shut down. In rats, it has been demonstrated that increased urinary excretion of proteins is the earliest and most sensitive marker of damage (Gumbleton and Nicholls, 1988). In 1983, under sponsorship from the IHF Chrome Chemicals Committee, Allied Corporation evaluated several possible first aid renal therapy approaches (Powers et al., 1984, 1986) and developed a suggested treatment. This relatively simple

procedure (involving timely administration of ascorbic acid) has since been adopted by both industrial physicians and poison control centers, and is credited with markedly reducing the fatalities in these cases while also presenting a treatment course with a wide margin of safety.

CARCINOGENICITY

Chromium carcinogenicity has proven to be a complex matter. That inhalation exposure to Cr(VI) can cause cancer is in no way an issue, but the mechanism involved, and the involvement of other valence states of chromium and influence of solubility, still very much are.

The mutagenicity of chrome compounds has been extensively studied (Petrilli and DeFlora, 1977), and is discussed elsewhere in this issue. Petrilli and DeFlora, (1978), among others, have demonstrated an inducible metabolic deactivation system for mutagenic Cr(VI) in mammals. Steinhoff et al. (1986a,b) and Rinehart and Gad (1986) demonstrated in a chronic rat bioassay that individual high exposures were necessary to induce respiratory cancers, with the same total life-span dose spread over smaller individual doses seemingly being handled by a metabolic defense mechanism. This case is presented in detail by Gad and Weil (1986). A recently reported pilot inhalation carcinogenicity study in rats (Glaser et al., 1988) supported the same differentiation.

Finally, there continues to be strong evidence that sparingly soluble chromates present a greater hazard than those that are either very water soluble or insoluble. It is my belief that this is because particles of such materials serve as high intensity point sources in the lungs, leading to a prolonged local insult at or above the level at which defenses are effective.

SUMMARY

- The key points of systemic chromium toxicity can be summed up as follows.
- Hexavalent chromium presents a greater hazard than other forms.
 - Chromates can be corrosive to the eyes and skin.
 - Chromates are sensitizers.
 - The kidneys are the target organ for systemically absorbed chromates.
 - Hexavalent chromium is a carcinogen, but acts by mechanisms which give it an effective threshold of effect.

REFERENCES

- American Conference of Governmental Industrial Hygienists (ACGIH), 1985. Threshold Limit Values and Biological Exposure Indices for 1985-86. ACGIH, Cincinnati, OH.
- Baetjer, A.M., 1950. Pulmonary carcinoma in chromate workers: 1. A review of the literature and the report of cases. *Arch. Ind. Hyg. Occup. Med.*, 2: 505-516.
- Cumin, W., 1827. Remarks on the medicinal properties of madar, and on the effects of bichromate of potass. on the human body. *Edinburgh Med. Surg. J.*, 28: 295-312.

- Environmental Protection Agency (EPA), 1984. Health Assessment Document for Chromium. EPA-600. 8-83-014F. EPA, Washington, DC.
- Fregert, S. and H. Rorsman, 1964. Allergy to trivalent chromium. *Arch. Dermatol.*, 90: 406-411.
- Gad, S.C., 1988. A scheme for the ranking and prediction of relative potencies of dermal sensitizers based on data from several test systems. *J. Appl. Toxicol.*, 8: 461-467.
- Gad, S.C. and C.S. Weil, 1986. *Statistics and Experimental Design for Toxicologists*. Telford Press, Caldwell, NJ, pp. 203-205.
- Gad, S.C., B.J. Dunn, D.W. Dobbs and R.D. Walsh, 1986a. Development and validation of an alternative dermal sensitization test: The mouse ear swelling test (MEST). *Toxicol. Appl. Pharmacol.*, 84: 93-114.
- Gad, S.C., W.J. Powers, B.J. Dunn, G.M. Hoffman, K.M. Siino and R.D. Walsh, 1986b. Acute toxicity of four chromate salts. In: D.M. Serrone (Ed.), *Chromium Symposium 1986: An Update*. Industrial Health Foundation, Pittsburgh, PA, pp. 43-58.
- Glaser, U., D. Hichrainer and H. Oldiges, 1988. Investigation of the lung carcinogenic potential of sodium dichromate and Cr(VI/II) oxide aerosols in Wistar rats. *Zentralbl. Bakteriol., B*, 185: 476-477.
- Gross, E. and F. Kosch, 1943. Lung cancer in chromate dye industry. *Arch. Gewerbepathol. Gewerbehyg.*, 112: 164-170.
- Gumbleton, M. and P.J. Nicholls, 1988. Dose-response and time-response biochemical and histological study of potassium dichromate-induced nephrotoxicity in the rat. *Food Chem. Toxicol.*, 26: 37-44.
- Industrial Health Foundation, 1981. *Proceedings of the Chromate Symposium — 80*. Industrial Health Foundation, Pittsburgh, PA.
- Korallus, U., C. Harzdorf and C. Lewalter, 1984. Experimental basis for ascorbic acid therapy of poisoning by hexavalent chromium compounds. *Int. Arch. Occup. Environ. Health*, 53: 247-256.
- Mackenzie, J.N., 1884. Some observations on the toxic effects of chrome on the nose, throat and ear. *JAMA*, 3: 601-603.
- Parkhurst, H.J., 1925. Dermatitis industrialis in a blueprint worker due to chromium compounds. *Arch. Dermatol. Syphilol.*, 12: 253-256.
- Petrilli, F.L. and S. Deffora, 1977. Toxicity and mutagenicity of hexavalent chromium for *S. typhimurium*. *Appl. Environ. Microbiol.*, 33: 805-809.
- Petrilli, F.L. and S. Deffora, 1978. Metabolic deactivation of hexavalent chromium mutagenicity. *Mutat. Res.*, 54: 139-147.
- Powers, W.J., S.C. Gad, M.J. Derelanko and K.M. Siino, 1984. Effects of therapeutic agents on chromium induced acute nephrotoxicity. *Toxicologist*, 4: 298.
- Powers, W.J., S.C. Gad, K.M. Siino and J.L. Peckham, 1986. Effects of therapeutic agents on chromium induced acute nephrotoxicity. In: D.M. Serrone (Ed.), *Chromium Symposium 1986: An update*. Industrial Health Foundation, Pittsburgh, PA.
- Rinehart, W.E. and S.C. Gad, 1986. Current concepts in occupational health: Metals — chromium. *Am. Ind. Hyg. Assoc. J.*, 47: 696-699.
- Serone, D.M., 1986. *Proceedings of the Chromium Symposium 1986: An Update*. Industrial Health Foundation, Pittsburgh, PA.
- Steinhoff, D., S.C. Gad, G.K. Hatfield and U. Mohr, 1986a. Carcinogenicity studies with sodium dichromate in animals. In: D.M. Serrone (Ed.), *Chromium Symposium 1986: An Update*. Industrial Health Foundation, Pittsburgh, PA, pp. 131-155.
- Steinhoff, D.G., S.C. Gad, G.K. Hatfield and U. Mohr, 1986b. Carcinogenicity study with sodium dichromate in rats. *Exp. Pathol.*, 30: 129-141.