

Chromium as an essential and toxic metal¹

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Chromium raises special issues related to its form-specific biological activity. Chemical form, oxidation state, and route of administration all appear to be important determinants of the essential and toxic actions of chromium.

Chromium is an essential metal. Reduction in intake below a critical level consistently leads to functional deficits, and supplementation consistently reverses these deficits (1). The principal sign of chromium deficiency is impaired glucose tolerance. Trivalent chromium, as a component of a low molecular-weight organic complex called the glucose tolerance factor, is believed to be the essential form of the metal.

Chromium is also toxic. Compounds of both hexavalent and trivalent chromium can cause allergic contact dermatitis, and hexavalent chromium is locally irritating and corrosive due to its acidity and oxidizing potential. Acute exposure of experimental animals to hexavalent chromium compounds leads to acute nephrotoxicity, which can be sufficiently severe to cause renal failure and death. In rats, both tubular and glomerular damage occur (2). Humans can also suffer renal tubular damage following massive exposure to hexavalent chromium (3). Systemic effects of chronic low-level hexavalent chromium exposure have been difficult to document in any species (4, 5). Systemic effects of trivalent chromium are not known. This inactivity has traditionally been attributed to an inability of trivalent chromium to traverse membranes and thus to penetrate into cells (6). However, recent work has shown that trivalent chromium can cross the cell membrane, although slowly, and that its entry into the cell is facilitated by the formation of diffusible complexes with low molecular-weight ligands (7). Hexavalent chromium, on the other hand, readily enters cells, probably via the anion transport system (8).

Hexavalent chromium is generally acknowledged to be a pulmonary carcinogen (9). The reduction of hexavalent chromium to the trivalent form occurs rapidly in all body fluids and tissues, including the lung and gastrointestinal tract, through a variety of enzymatic and nonenzymatic processes. These reduction processes generate reactive intermediates that may be the cause of pulmonary carcinogenicity (10) and possibly of other forms of toxicity. Therefore, two critical factors in any evaluation of chromium toxicity and kinetics are the site(s) and rapidity of reduction of hexavalent chromium to trivalent chromium and possible portal-of-entry differences related to the rate of this reduction process and to the relative abilities of hexavalent and trivalent chromium to penetrate membranes and, consequently, to be absorbed into systemic circulation.

Taken orally, soluble hexavalent chromium is believed to be almost entirely reduced to trivalent chromium before reaching sites of absorption in the small intestine, where trivalent chromium is very poorly absorbed when compared with hexavalent chromium. In the lung, soluble hexavalent chromium is absorbed into the systemic circulation at least partly as hexavalent chromium (11). Thus the oxidation state is a critical factor determining not only the toxicity of chromium, but also its route-dependent bioavailability.

A third major factor is solubility, which can differ greatly in the lung and in the strongly acidic stomach contents. Soluble hexavalent chromium compounds are rapidly cleared from the lung with significant uptake into the systemic circulation, while poorly soluble compounds are cleared slowly, primarily into the gastrointestinal tract, with little or no systemic uptake (12). Experimental evidence suggests that chromium compounds of intermediate solubility may be the most carcinogenically active in the lung, since they provide a reservoir of hexavalent chromium for low-level but persistent generation of the chemically reactive intermediates (13).

A physiologically based model of the absorption and disposition of chromium in rats has been developed in an attempt to quantify some of the issues surrounding the route and oxidation-state dependence of chromium disposition. The basis of the model is a general model of rat body and bone growth from birth to maturity (14, 15). It consists of liver, kidney, gastrointestinal tract, lung, bone, well-perfused

¹ Extended abstract: full report to be published in Olin S, ed. *Risk Assessment of Essential Elements: Proceedings of a Conference on Risk Assessment of Essential Elements*, Herndon, Virginia. In press.

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tissues, and poorly perfused tissues. Incorporation of chromium into bone and its release from bone are taken into account. The exchange of hexavalent chromium with tissues is considered to be flow-limited, while the exchange of trivalent chromium with tissues is assumed to be diffusion-limited. The reduction of hexavalent chromium to trivalent chromium is modeled in all tissues except bone, as well as the gastrointestinal tract and lung. A working version of the model has been presented elsewhere (16).

The model is currently in the process of validation by comparison of model simulations with data from studies of the kinetic behavior of trivalent and hexavalent chromium given by intravenous, oral, and intratracheal instillation, or by inhalation. In general, the kinetic behavior of chromium is consistent with the understanding of the factors that govern absorption, distribution, and elimination. The results of studies in which chromium was administered as salts of different oxidation states and by different routes are also reasonably consistent with one another and with a single physiologically based model of chromium kinetics.

Development of this model was supported by contract F33615—85—C—0532 from the United States Air Force.

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