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# Setting the Research Agenda for Chromium Risk Assessment

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The process of assessing the public health risk of exposure to particular environmental contaminants is complicated and full of assumptions and uncertainties (*1,2*). However, the problems of assessing risks for chromium exposure are unusually complex (*3,4*). The problems posed by current investigations of chromium-contaminated soil in northern New Jersey (*5*), in part, provided the impetus for a conference on a research agenda for chromium contamination and risk assessment.

During the first half of the present century, northern New Jersey was the chromite-chromate industrial capital of the world, and we face today the legacy of chromium-containing slag left by this industry and distributed gratis to many locations and communities in Hudson County. The magnitude of this waste problem measured in millions of tons at dozens of sites is staggering (*5*), but this conference (to the disappointment of some) is not about New Jersey *per se* but about the generic environmental health problems posed by chromium in the environment and the resultant human exposure and health risks.

Chromium, because of its unique properties, was rapidly exploited for many purposes, first as a mordant and oxidizer in the dyeing industry, later in tanning, and then in metallurgy for its alloying properties with iron, and even more recently for its metal-plating properties (*6*).

Chromium has been in commercial use for less than 300 years. It is a rather rare mineral in the earth's crust, with only a few deposits around the world proving economically exploitable. Although it does not have a long history comparable to lead, iron, or mercury, for example, it appears to be making up for this lack of history by providing major challenges for exposure and risk assessment and public health policy.

The greatest challenge of chromium for the risk assessor, and certainly for the risk communicator, lies in the differential toxicity and carcinogenicity of trivalent and hexavalent chromium (*7*). For the risk communicator, the fact that hexavalent chromium is a potent carcinogen while trivalent chromium is an essential trace element poses a major problem. It is not surprising that lay persons would be troubled by this paradox, but it would be far simpler for the professional if one could ascertain with confidence whether a particular exposure scenario involves primarily the hexavalent or trivalent form. To complicate matters, among hexavalent salts it appears to be the partially soluble salts (i.e., zinc chromate) that are more carcinogenic than either the insoluble salts (e.g., lead chromate) or the soluble ones (e.g., sodium or potassium chromates and dichromates) (*8*).

The fact that chromium exists in several oxidation states in the environment and the body is certainly not unique. However, the propensity of chromium to change oxidation states, both in environmental media and in living cells, requires far better understanding of the redox environments and poses a major challenge to the analytical laboratory. Two different laboratories analyzing the same soil sample have been known to report the chromium content as almost entirely hexavalent in one case and entirely trivalent in the other. Even a novice may guess that this discrepancy arises from different ways of handling, digesting, or extracting the sample, such that oxidation (or reduction) may occur in the laboratory itself. But clearly, research is required to establish sound and reproducible analytical protocols that can be replicated reliably in standard environmental laboratories. These must apply not only to air and water but to complex environmental and biological matrices. Thus, an examination of the research needs for analysis of chromium was recognized as one major focus of the conference.

The process of risk assessment is outlined in various ways, partially depending on whether one focuses on cancer or other health end points. However, the general format involves four steps (*1*) variously referred to as follows:

*a*) hazard identification and evaluation (determining one or more hazardous substances and defining the end points of interest);

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*b*) hazard quantification or dose-response determination (reviewing toxicologic and epidemiologic literature to relate particular responses to particular levels of exposure or dose);
*c*) exposure assessment (completing an exposure matrix that takes into account the routes of exposure and the media of exposure and establishing exposure scenarios);
*d*) risk characterization (or analysis or estimation) in which one combines the dose-response information with the exposure assessment to determine the level of risk to one or more target populations under one or more exposure scenarios.

A comprehensive risk assessment involves the consideration of several sources or routes of exposure and different target populations with different exposure contexts (durations or conditions of exposure) and different susceptibilities (children, workers, asthmatics, etc.). Yet often only one or two components turn out to drive the risk assessment, contributing the major risk to the overall estimate. Certainly for industrial exposure scenarios, inhalation of hexavalent chromium leading to lung cancer turns out to be the major component of the overall risk, and the only one dealt with in many studies. However, for community exposure to chromium-contaminated soil, inhalation is less likely to dominate the exposure scenarios unless the soil is dry and dusty. Ingestion of soil by children, for example, may turn out to dominate the risk assessment as it does for 2,3,7,8 tetrachlorodibenzo-*p*-dioxin-contaminated soil (*9*).

Clearly, the process of hazard identification for chromium requires accurate determination of the oxidation state of the compound in nature, as well as identification of which hexavalent salt(s) is present. Establishing the form and content of a toxic material in environmental media is the first requisite for understanding its health consequences. What happens to the chromium when it enters the body is also important for several reasons.

It is well established that $Cr^{VI}$ is a lung carcinogen (*10*), with some studies (particularly early ones) of chromium-exposed workers showing a relative risk of more than nearly 20-fold (*8,11*). Yet it has proven very difficult to mimic this in animal models. A reliable inhalation model for $Cr^{VI}$ and pulmonary carcinogenesis remains to be developed, and since positive results were achieved with calcium chromate but not with soluble chromates, attention should focus on those chromates already implicated as carcinogens in epidemiologic studies (*3,8*). Moreover, although we know that inhalation of hexavalent chromium is associated with a high risk of lung cancer, both epidemiologic and toxicologic research to date are unclear on the cancer potential associated with ingestion or dermal absorption of hexavalent chromium compounds or on the cancer risk to other organ systems.

Since in many risk assessments, particularly where children are involved, soil ingestion may be a primary route of exposure, this raises the question of the cancer risk associated with ingestion of hexavalent compounds. Understanding how chromium behaves in the body, and particularly how the genotoxic effects of chromium are manifested, is therefore of particular importance. It is a reasonable guess that the potent carcinogenic effect of hexavalent chromium is somehow related to the redox reactions that proceed in the cell. The fact that hexavalent chromium freely enters cells, while trivalent chromium apparently does not, raises additional questions regarding the mechanism of chromium toxicity and carcinogenicity.

Understanding the mechanisms of chromium carcinogenicity is an important requirement for designing a risk assessment, while obtaining better epidemiologic or toxicologic evidence regarding the carcinogenic effects by routes other than inhalation is clearly another research priority.

Similarly, there is a need to sort out the impact of dermal exposure and dermal absorption of chromium. Although occupational dermatology has traditionally distinguished between sensitization and irritation in causing contact versus irritant dermatitis, it is not at all clear how this distinction operates in the case of chromium since some compounds are suspected of being potent sensitizers whereas others are know irritants. Moreover, if dermal responsiveness to chromium is widespread, it (rather than cancer) may prove to be the health effect that drives policy regarding mitigation and reduction of exposure. Setting a research agenda for chromium is not intended to solve specific environmental chromium problems, but to identify what information we need in order to make sound judgments regarding chromium in our environment or chromium in our lives.

Ultimately, to make sensible decisions about risks associated with chromium in the environment it is essential to *a*) establish the form and quantity of chromium in the environment and assess its bioavailability; *b*) establish the routes of exposure and how these might affect the chromium species to which individuals are exposed; *c*) distinguish each of the exposure sites, skin, lungs, and intestinal tract, as target organs on the one hand or routes of exposure on the other; *d*) understand the mechanisms by which the different chromium species exert toxic effects and the conditions under which these effects are manifest. This conference is designed to identify those components of the puzzle that require further research attention.

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