

# Panel Discussion: Epidemiologic and Toxicologic Studies of Chromium\*

by Michael Gochfeld†

## Introduction

The questions posed to the panel focused mainly on methods of exposing experimental animals and on the dermatologic consequences of chromium exposure. The role of bioavailability figured prominently in both issues. Individuals whose homes or workplaces are on former chromium-waste dumpsites and particularly children who play on such sites are likely to have skin contact with chromium compounds. If they are exposed at all it would be to a relatively low dose, but exposure is likely to be recurrent, and the skin may be the main route of exposure. For children, however, ingestion cannot be ignored.

## Intestinal Dosing and Bioavailability

Various approaches have been used to expose experimental animals to chromium. With respect to intestinal absorption of chromate, questions were raised regarding the choice of vehicle. C. Witmer (Rutgers University) noted that in her studies she used water as the vehicle for the sodium salt because it was soluble and used corn oil for the less soluble calcium chromate and for preparing a soil slurry. She noted that researchers need to take into account the impact of different solvent conditions as well as the pH of the mixture relative to intestinal pH in designing such experiments.

With respect to the choice of gavage over feeding, Witmer added that feeding experiments with rodents are complicated. Animals do not eat in a way that allows delivery of a quantitative dose. They spill food and water, and higher doses of chromium depress feeding, thereby affecting the actual doses delivered. It is most desirable to develop a pair-feeding study, ideally using metabolic cages.

Absorption is a critical element in exposure. In response to a question on absorption, Witmer noted that the animals were given the doses in the morning when they probably had an empty stomach and that absorption from a full stomach would probably be different.

F. Kauffman raised the more general question about whether we can really say anything about the actual public health magnitude of the problem associated with chromium contaminated soil.

P. Lees (School of Hygiene and Public Health, Johns Hopkins University) responded from an industrial hygiene perspective, noting that it is essential to understand the exposure of the population. Taking Jersey City as an example, he noted that the fact that the chemicals are present is only the first step. The systematic studies on exposure, uptake, and bioavailability have yet to be made in Jersey City or elsewhere. It is essential to characterize the concentrations in dust and to know the proportion that is on respirable particles. This would provide information on the contribution of inhalation to risk. However, it is even more difficult to figure out what is ingested or absorbed through the skin, and he concluded that developing improved measures of exposure is a high priority.

Questions were raised regarding the adequacy of the epidemiologic data base. L. Bidstrup summarized recent studies of chromate-exposed workers in Europe which show only a slightly elevated lung cancer risk at current exposure levels. In her long-term study, the excess lung cancer risk has declined from 3.6 times background in the days before process changes were made that reduced exposure, to only about 2.0-fold excess today.

R. Albert (University of Cincinnati) noted that the earlier chromate cohorts showed much higher relative risks. He cited a Mancuso study (1) where measurements were made which allow risk estimates in terms of a Q1\* (cancer potency) value. He concurred that the exposure assessment remains the major unknown area. He noted that it would be no surprise if the level of risk in more recent studies were lower, and he observed that in the recent study reported by Bidstrup, a major

\*Moderator: Michael Gochfeld. Panelists: Robert Bagdon, Peter Lees, Roy Albert, and Charlotte Witmer. Participants from audience: Robert Adams, Leslie Bidstrup, Robert Hazen, Paul Lioy, Ron Corcoran, Barbara Gerwel, and Fred Kauffman.

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source of hazard—the use of lime—had been eliminated. Lime in the process leads to formation of the partially soluble calcium chromate salt, which has a high cancer potency.

M. Gochfeld (UMDNJ-Robert Wood Johnson Medical School) suggested that the use of calcium chromate in some animal studies and soluble chromates in other studies may account for difficulties of showing lung cancer in animals. Studies using calcium chromate were positive.

Gochfeld indicated that even within the chromate production industry, companies differed with respect to their actual manufacturing processes and their investment in safety and cleanliness. All of these would be expected to change over time. So it should not surprise anyone that the earlier studies would have the higher relative risk. Future studies should determine whether the chromate cohorts experience reduced risk, the further removed they are from exposure, much as occurs with former smokers whose lung cancer risk approaches that of new smokers after about 15 years since smoking cessation.

There remains, however, a discrepancy between the U.S. studies which showed standardized mortality ratios (SMR) for respiratory cancer in excess of 20 and Bidstrup's studies in Britain where the SMR was not more than 4.

## Chromium Sensitivity in Industrial Cohorts

R. Adams, author of a major textbook on occupational dermatology, pointed out that much of what we know about the dermal effects of chromium comes from studies of industrial groups, particularly those engaged in manufacturing cement. These workers are exposed to chromium, but also experience significant skin irritation from the cement itself. This irritation potentiates the effects of chromium and appears to increase the likelihood of sensitization.

Gochfeld remarked that there are two components to understanding reactivity of the population of chromium. First, given that all members of a population are exposed to a high level of chromium (for example, soil concentration of 1000 ppm), what percentage will become sensitized? Secondly, assuming that you have a subpopulation in which all persons are sensitized, how many will show a positive reaction to a particular dose—or what is the dose-response curve for skin reactivity?

The problem with chromate, Adams noted, is the same as the problem with formaldehyde and other contact allergens. Everybody's skin is different with respect to texture and reactivity. It's hard for novices to distinguish an irritant reaction from an allergic reaction. Adams reported that there is less contact sensitivity to chromium today than 20 years ago because less chromium is used at this time, and he remarked that many of the early responses were probably irritant reactions.

Adams noted that based on data from referral clinics

which see patients who already have some kind of dermatitis, about 2.6% test positive to chromium. He presumes that this is much higher than the proportion in the general population, which he suspected would be less than 0.1%, but he noted that we clearly need to collect this data. From years of experience in patch testing many patients with chromium, about 1 to 2% test positive, which compares pretty favorably with other contact allergens.

Albert asked what proportion of workers develop chrome dermatitis. Adams suggested that it is a very small percentage, probably about 1% or less. He noted that cement workers have years of irritant dermatitis, yet sometimes it takes 20 to 30 years to become sensitive to chromium despite the dermatitis. Adams acknowledged that there is only a small level of chromium in cements (about 0.2%), but even at that low level, with an irritant dermatitis there is a risk of getting sensitized. Overall, the studies of cement workers indicate that 8 to 9% are allergic to chromium on patch testing but have not history of dermatitis.

Gochfeld reiterated that the self-selection phenomenon probably means that those workers who became sensitized more easily or responded more strongly removed themselves from exposure by choosing other work and therefore would not have been seen in the clinical setting, and Adams concurred that this could well have been the case in his cohort.

## History of Patch Testing

Adams agreed that we need to know a great deal more about chromium. He noted that historically, patch testing was first performed around the turn of the century, while in the U.S. the first skin test for chromium was applied in 1925. The first patient tested was a blueprint operator who developed a severe dermatitis from contact with the blueprint solution, which happened to be potassium dichromate. The patient was tested with a 0.5% chromate solution, and there was a strong positive reaction. Adams pointed out that epicutaneous or patch testing is still the main standby for determining delayed skin hypersensitivity or type IV sensitivity.

## Improved Approaches to Testing

R. Bagdon (UMDNJ-Robert Wood Johnson Medical School) emphasized that it is desirable to improve the standard patch testing procedure so that it can be applied in a prognostic fashion to determine whether a community population is prone to becoming or has become sensitized to chromium. He recommended modifying the patch test to deliver the challenge dose by iontophoresis. This would allow administration of the dose in a short time period (approximately 30 min) and would allow administration of a precisely regulated challenge dose, allowing much more accurate quantification than a passive diffusion patch test.

Bagdon noted that we really do not know about the

effective dose. People are patch tested for several hours with chromium in petrolatum and water, and the presence of the lipid may not be a perfect model for environmental dermal exposure. Since we really do not know what we would see with 1000 ppm hexavalent chromium, it is important to approach the problem using the patch titration method that he described earlier. Where 0.5% down to 0.001% is used, we would expect to see a general decrease in susceptibility to the decreasing doses. The traditional patch test is most useful in confirming a clinical diagnosis, which is quite different from using it as a prognostic indicator in a population or an individual to determine whether at some time in the future a full blown clinical dermatitis will occur.

Adams cautioned, however, that standardization of a technique is crucial and that any new approaches should be validated by running them in tandem with a standard patch test. "It's the best test we have, and it's the only test we have." He noted that he began testing for chromium in about 1965 when the North American Contact Dermatitis group was established. The use of a 0.5% chromate solution, the same concentration used in the first test in 1925, continued until about 1988, when the concentration was reduced by consensus to 0.25%. However, in Europe, patch testing for chromium sensitivity is still done with a 0.5% solution, and the appropriate dose remains a matter of debate. Adams indicated that at 0.25% one will miss cases of chromium sensitivity.

## Selection of Appropriate Doses

A question was raised regarding patch testing with a more realistic dose, such as 0.1% or 0.05%, which represents the concentrations present in some of the soil at contaminated sites rather than the industrial concentrations. R. Corcoran noted, however, that there are places in Hudson County, New Jersey, where the soil concentration is actually as high as 1 to 4% at the soil surface where people are working or children are playing. There is often abrasion or other interruption of skin integrity so that the opportunity for chromium sensitization appears very real.

Adams also objected to the use of much lower doses, noting that even at the present 0.25% concentration we are likely to miss some allergy, although there is some benefit from reduced irritation. Most people who are going to respond will be sensitive between 0.1% and 0.25%, and that is what you want to reach.

Bagdon described the existing dose-response information based on the patch titration studies of various concentrations. At 0.01% concentration the proportion of positive reactions was 13%. This increased to 26% with a 0.05% concentration and 40% with a 0.1% concentration, while with 0.001% the response rate is about 1 to 3%. He speculated that if you used a 0.001% patch test on a population of 100 people who were already sensitized to chromium and had a diagnosis of dermatitis, you would get about 10% reactors, then the corresponding threshold concentration would be 0.001%. It would

be important to know how this related to concentrations in soil.

R. Hazen noted that it is difficult to compare concentrations in soil to concentrations in solution. It is essential to understand how much of the material is available to react in the skin to elicit the allergic reaction. He noted that analytic data suggest that much of the hexavalent chromium would be available to reach the skin.

## Relevance of Patch Testing to Dermal Sensitization

Albert noted that two points were being confused. The focus should not be on the odds of a person with no dermatitis showing up with a positive patch test, but on the risk of an exposed person developing dermatitis. For example, what is the risk to a little child playing in soils with concentrations above 1000 ppm of developing chromium dermatitis?

Bagdon and Adams concurred that at present we do not know the risk of sensitization, but it is certainly not negligible. We know somewhat more about the dose-response curve for people who are already sensitized.

Gochfeld concluded that there appear to be two different dose-response issues, the traditional one of the response of sensitized individuals to different concentrations or exposure levels of chromium and the response curve for a normal population becoming sensitized in the first place. The sensitization dose-response curve is likely to look very different from the dermatitis dose-response curve in sensitized people, which again will be different from the dermatitis dose-response curve in population whose sensitization status is not known.

Bagdon noted that there is some evidence regarding dose-response curves. For example, once sensitized, less than 10% of people respond to a 0.001% challenge, and this seems to be consistent across occupational studies.

## Process of Sensitization

Chromium sensitivity is a type IV delayed hypersensitivity. The reaction is stimulated by haptens, which have a molecular weight usually less than 500 and which must combine with protein in the skin to stimulate the development of the sensitized lymphocytes.

Gochfeld asked Adams if the general public in their daily lives were exposed to dermal application of chromium, would he anticipate a substantial number becoming sensitized. Adams responded, "We really don't know. One of the big problems with chromium is that humans who are already sensitized respond at a very low level. We're not absolutely certain about the total in the population that could be made sensitive." He added that in the U.S., chromium exposure is almost exclusively occupational, although in Europe it is thought to be present in some detergents and that may be why in nonoccupational populations chromium dermatitis is more common in women.

He offered as an example that about 9% of the women

in this country are probably allergic to nickel from ear piercing. The pierced ear provides a route of access for the nickel in the earring to sensitize the skin. He compared this frequency with about the 70% of the population that is reactive to poison ivy (*Rhus dermatitis*).

P. Liroy noted that even if there is a very low rate of positive responses on patch tests, the risk of becoming sensitized and subsequently developing dermatitis may be high if many people are exposed to a large amount of material. In other words, from a public health perspective it is just as important to be concerned with the absolute magnitude of the risk (number of people becoming ill) as with the relative risk. He believed that studying the dermal exposure and sensitization issue should be given high priority.

### Are Children at Increased Risk of Sensitization or Dermatitis?

Where children are involved it is essential to know whether they have increased likelihood of becoming sensitized to contact allergens. Children's skin is different from adult skin, and of course, their play behavior increases their dermal exposure. Gochfeld noted that up until about age 2, infants are believed to be at greater risk of sensitization to ingested antigens. Bagdon noted that young animals are also more readily sensitized than adults. Clearly, it is necessary to determine the extent to which children are more readily sensitized than adults, and Adams added, "Is the question whether they are more readily sensitized, or once sensitized whether they respond at a lower dose" and concluded, "I don't know the answer to that."

A speaker suggested that children living in Jersey City are exposed like a worker, but they live there all day long, hence, sensitivity in the community study needs to be handled differently from a traditional clinical study or industrial cohort. Gochfeld remarked that not only is a 168 hr/week exposure different from a 40-hr exposure, but the latter allows some time for readaptation and reduction of exposure, hence the community exposure is more than four times greater than workplace exposure.

### Sensitization to Hexavalent and Trivalent Chromium

Adams noted that with poison ivy exposure the pure pentadecyl catechol is a very effective sensitizer. By contrast, hexavalent chromium is present at very low levels, so its sensitization potential at different doses would have to be explored. Also, trivalent chromium is not a good sensitizer. For a clinician it seems important to know how much hexavalent chromium is present in the soil and whether that is enough to sensitize individuals who have not been sensitized before. We know that many people who work with higher concentrations of chromium, for example, in electroplating or cement work, do not develop sensitization or at least do not manifest contact dermatitis.

Liroy emphasized that this could be due to a self-selec-

tion process in the workplace. If you become ill you do not continue working but switch jobs. This option is not available if you live in a community where chromium exposure occurs.

### Risk Factors of Sensitization

B. Gerwel explored the issue of risk factors influencing a person's ability to be sensitized. Adams noted that no one is born with sensitivity to chromium. It is developed and this has to do with many factors, for example, whether or not there is irritation of the skin to start with and what the concentration is. Chromium sensitivity is the number one sensitivity in cement workers, but they seem to develop it after many weeks or even years of irritation, which allows the chromium to get into the skin and produce the allergic reaction.

The panel concurred that whatever information we have on sensitization has to do with the environmental components, such as methodology, vehicle, concentration, and irritation, and not with a person's underlying genetic or epigenetic susceptibility to chromium or any other contact allergens. Gochfeld remarked that in general our understanding of variation in human susceptibility to any agent is meager.

### Reactivity of Sensitized Individuals

A question was raised over which was more important, the absolute mass of material contacting the skin or the concentration. The panel concurred that since the material is not absorbed into the body, concentration is probably more important in determining reactivity. Thus, a 2- $\mu$ g dose spread over a wide area will not have the same effect as 2  $\mu$ g administered under a patch. Adams noted that patch test results can vary depending on the vehicle, pH, or matrix used. Other variables are how long the patch is in place (24–48 hr), how long after removal of the patch one reads the reaction, and the expertise of the reader.

Adams noted that there are only very limited data for comparing response to absolute mass in skin, so from a clinical point of view (e.g., surveillance of a population), concentration is the critical thing. With respect to concentration in soil, "I doubt that we have the data to be able to extrapolate from a soil matrix to a population."

The follow-up question was what happens if exposure occurs over a large area of the body, so that the mass contacted is high. Again, whether a particular area of the body responds depends on the dose reaching it, which is a function of the concentration.

### Is There Epidemiologic Evidence of Elevated Dermatitis?

Bidstrup asked whether there is any evidence that there is a high incidence of contact dermatitis in this part of New Jersey, and Gochfeld remarked that more research is needed on this topic. If one were dealing

with mortality or with reportable diseases such as cancer, these data would be available, and indeed one could compare events on a township-by-township basis. However, there is no data base for dermatitis. One would have to develop a surveillance system, contacting physicians who might see such patients. Since mild contact dermatitis does not necessitate a visit to a dermatologist, one would have to use a broad net to pull in the cases and thereby determine whether there is an excess in northern New Jersey.

## Is a Generic Approach to Chromium Risk Possible?

One participant inferred that given the complexities both in the environment and the body, it appears to be necessary to study exposure on every chromium site that exists. Gochfeld interpreted this as a challenge to the group, that is "to what extent can our science have a predictive element. Can we develop generic principles such that we do not have to study every new site *de novo* as a unique entity? Perhaps it is not possible to develop

a generic approach. In that case science is not contributing the way it should be."

The panel concurred that carefully controlled testing by experienced investigators would be necessary to determine the extent to which a particular population has already been sensitized as well as the dose-response curve for sensitized individuals. One problem is whether the testing itself carries with it a finite risk of sensitizing individuals.

Overall, the panel session identified *a*) the need to improve our understanding of bioavailability, both for toxicologic studies and for human exposure studies; *b*) the need to improve our understanding of human susceptibility to chromium sensitization; and *c*) the need to establish dose-response curves both for initial sensitization and for dermal reactivity of sensitized individuals.

## REFERENCE

1. Maneuso, T. F. Considerations of chromium as an industrial carcinogen. In: Proceedings of the International Conference on Heavy Metals in the Environment (T. C. Hutchinson, Ed.), Institute for Environmental Studies, Toronto, 1975, pp. 343-356.