ITER Peer Review on Hexavalent Chromium
Meeting Summary

April 16, 1998
Conference Call

A reference concentration (RfC) for hexavalent chromium was reviewed by a panel of risk assessment experts on December 16, 1996. At that meeting the panel raised a number of issues and concerns which it asked the authors (ChemRisk Division of McLaren/Hart) to address in a revised document. This same panel of reviewers discussed this revised document in a conference call on April 17, 1998. This conference call was organized by Toxicology Excellence for Risk Assessment (TERA), a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessment. For a complex assessment such as this, each reviewer brought to the review his or her particular expertise, which when combined, provided a comprehensive overall review of the assessment document.

The peer review conference call began with a discussion of conflict of interest. Prior to the first meeting in December 1996 each reviewer certified that he or she did not have a conflict (real or apparent) with the chemical under review, or with the sponsor. Reviewers represent their own personal scientific opinions, and not those of their employers. Possible conflicts were discussed with the reviewer to determine if measures were needed to manage the conflict (or appearance). Options include excluding the reviewer from that chemical's discussion and consensus, or allowing the reviewer to participate in the discussion, but not be polled for consensus. The peer review panel discussed the original certifications again, and agreed upon how to manage any potential conflicts. This discussion is documented in Attachment A.

These reviews follow a standard format, beginning with a close examination of the supporting documentation and important references several weeks prior to the meeting. At the meeting or conference call, a discussion of conflict of interest and decision by the panel occurs, followed by a briefing by the authors of the assessment. The panel then systematically discusses the assessment. For this conference call the outstanding issues identified at the December 16, 1996 meeting formed the basis for the discussions. Full discussion and participation are encouraged and agreement is reached by consensus. Consensus for the purpose of these meetings is defined as "an opinion held by all or most, or general agreement."

The conference call was open to the public and an individual from the U.S. Environmental Protection Agency took part.

Reference Concentration for Hexavalent Chromium

Sponsor:
ChemRisk Division of McLaren/Hart for:
Elementis Chromium, Corpus Christi, TX
Chemical Land Holdings, Dallas, TX
PPG Industries, Inc., Pittsburgh, PA

Presenter:
Ms. Deborah Proctor, ChemRisk Division of McLaren/Hart

Chair:
Dr. Michael Dourson, Toxicology Excellence for Risk Assessment

Review Panel:
Dr. Stuart Baxter*, University of Cincinnati
Dr. Robert Benson, U.S. EPA
Dr. Matthew Bogdanffy, Haskell Laboratory, DuPont
Dr. John Christopher, California EPA
Dr. Gary Diamond, Syracuse Research Corporation
Dr. Michael Dourson, Toxicology Excellence for Risk Assessment
Dr. Linda Erdreich, Bailey Research Associates, Inc.
Dr. Marvin Friedman*, Cytec Industries, Inc.
Dr. Michael Gargas*, ChemRisk Division of McLaren/Hart
Dr. Kenneth Poirier, Procter and Gamble
Dr. Andrew Renwick*, University of Southampton

* These reviewers were not able to participate in this conference call due to scheduling difficulties and therefore, their opinions are not reflected in this document. They were present at the first meeting.

Dr. Michael Dourson, as Chair, began the meeting by suggesting a process for conducting the conference call that would facilitate an efficient discussion. The panel agreed to follow a process whereby each of the six issues identified from the first meeting would be discussed in order. Dr. Dourson called upon a different individual peer reviewer to begin each issue's discussion with his or her opinion on whether or not ChemRisk answered the question or issue as identified, and whether he or she agreed with the ChemRisk position. The discussion was then opened to others, with an alphabetic roll call used to solicit each reviewer's opinion. Opportunity for ChemRisk to respond to the peer reviewers' comments was also provided. Observers were offered the opportunity to present technical comments.

ISSUES FROM THE DECEMBER 16, 1996 MEETING

Issue 1. Provide a clearer distinction of the different forms of chromium the RfC is for and perhaps consider developing different RfCs for acid mists and dust containing hexavalent chromium.

Issue 2. Add a more complete discussion of all available animal and human studies, as well as ongoing research.

Issue 3. Investigate further the upper respiratory tract toxicity and attempt to obtain raw data from Glaser.

Issue 4. Consult with an immunologist regarding the significance of the immune effects observed in Glaser et al. (1985).

Issue 5. Determine which deep lung effects should or should not be combined in order to use as basis of critical effect. Acknowledge that both the lactate dehyrogenase (LDH) and lung weight endpoints have weaknesses.

Issue 6. Use the default uncertainty factor of 10 for use of a subchronic study, unless better support for reducing this to three can be provided. The uncertainty factors for intra- and interspecies are appropriate as proposed. An uncertainty factor for database may not be needed, but needs better justification.

PRESENTATION

Deborah Proctor of the ChemRisk Division of McLaren/Hart presented the revised assessment of hexavalent chromium to the panel, focusing on the changes made in the document in response to the issues raised at the December 1996 meeting.

Issue 1. Provide a clearer distinction of the different forms of chromium the RfC is for and perhaps consider developing different RfCs for acid mists and dust containing hexavalent chromium.

The documentation package was revised to indicate that the proposed RfC is only for hexavalent chromium present in the environment as chromate salts, which are stable in the environment. Even though chromic acid is likely to be the most toxic form of hexavalent chromium, it is not stable in the environment and not thought to result in environmental exposures. Therefore, chromic acid is not the basis for the RfC.

Issue 2. Add a more complete discussion of all available animal and human studies, as well as ongoing research.

In response to this issue, the documentation package was revised to include a comprehensive Hazard Identification section and tables which summarize all human and animal studies available on the health effects of hexavalent chromium exposure.

Issue 3. Investigate further the upper respiratory tract toxicity and attempt to obtain raw data from Glaser.

In response to this issue, Dr. Glaser was contacted to determine if any additional data regarding upper airway irritation were collected, but not reported in Glaser et al. (1986), the 18-month cancer bioassay. Dr. Glaser indicted that the only upper airway irritation observed was reported in the manuscript. In addition, the revised documentation package now provides a focused discussion of all information regarding upper respiratory tract toxicity.

Issue 4. Consult with an immunologist regarding the significance of the immune effects observed in Glaser et al. (1985).

In response to this issue, Dr. Alice Wong, an immunologist at the University of California, Davis, was contacted to assist in interpreting the immune effects observed in Glaser et al. (1985). Dr. Wong stated that the immune effects observed could indicate a Type I allergic reaction, such as asthma, or they could be a normal immune response to a foreign body or inflammation. The revised documentation includes a discussion of the hexavalent chromium levels which induce asthma. In addition, the effects on total serum immunoglobins observed in Glaser et al. (1985) were included in the benchmark dose analysis for the revised RfC.

Issue 5. Determine which deep lung effects should or should not be combined in order to use as basis of critical effect. Acknowledge that both the LDH and lung weight endpoints have weaknesses.

The revised RfC was calculated based on the arithmetic average of the individual RfCs for several endpoints which represent the critical effect, lung inflammation. The endpoints averaged include lung weight, spleen weight, protein in bronchio-alveolar lavage fluid (BALF), albumin in BALF, total immunoglobins, and lactate dehydrogenase (LDH) in BALF. The benchmark dose analysis was conducted using both a polynomial mean response model and a power mean response model. LDH in BALF fit both models well; therefore, this endpoint was retained for RfC derivation as a relative endpoint suggestive of inflammation.

Issue 6. Use the default uncertainty factor of 10 for use of a subchronic study, unless better support for reducing this to three can be provided. The uncertainty factors for intra- and interspecies are appropriate as proposed. An uncertainty factor for database may not be needed, but needs better justification.

In considering the appropriate uncertainty factor for extrapolating from a less than chronic study, the following factors should be considered: accumulation/cumulative damage, pharmacokinetics/pharmacodynamics, severity of effect, recovery, duration of study, and consistency of effect within duration. For hexavalent chromium, only the accumulation and potential cumulative damage suggest that subchronic data may not be

representative of chronic exposure. An uncertainty factor of 3 is justified to account for this uncertainty because fibrosis, the ultimate outcome of inflammation, was not observed in the 18-month bioassay and because none of the endpoints showed an increased in effect between the 30 and 90 day exposure periods at the lower dose groups.

DISCUSSION

Issue 1. Provide a clearer distinction of the different forms of chromium the RfC is for and perhaps consider developing different RfCs for acid mists and dust containing hexavalent chromium.

The panel unanimously agreed that this issue was completely resolved and that the package clearly indicated that the RfC applies only to environmental exposure to hexavalent chromium salts and not to occupational exposure to chromic acid. Some reviewers disagreed with the statement that chromic acid is not an environmentally relevant form of hexavalent chromium. The panel recommended that the documentation should state that the RfC is protective of exposure to both mono- and dichromate salts. Reviewers noted that the documentation states that the RfC is also protective of exposure to both soluble and insoluble salts because the insoluble salts are less toxic; however, the documentation should include the evidence to support this statement.

Issue 1 is resolved. The documentation can be strengthened by clearly showing the support for the statement that the RfC is protective of exposure to insoluble salts because they are less toxic than the soluble salts.

Issue 2. Add a more complete discussion of all available animal and human studies, as well as ongoing research.

Overall, the panel reached unanimous consensus that this issue has been resolved and that the documentation package adequately describes all of the human and animal studies on hexavalent chromium. One reviewer suggested that the discussion of the human studies could be strengthened by improving the evaluation of the quality of the human studies. In addition, this reviewer noted that the discussion of some of the immunotoxicity data was misleading because case reports of single patients are not necessarily reflective of effects in the entire population. Another reviewer suggested addressing this by adding a column to Table 1 which shows the number of study subjects.

Issue 2 is resolved. The documentation can be strengthened by providing an introductory statement for the human studies as was done for the animal studies and by including a discussion of the quality of the human studies.

Issue 3. Investigate further the upper respiratory tract toxicity and attempt to obtain raw data from Glaser.

The panel reached unanimous consensus that no additional data are available on upper respiratory tract irritation and that the upper respiratory tract is not a critical target organ following exposure to hexavalent chromium salts. This issue has been resolved.

Issue 3 is resolved. No additional work is recommended for this issue.

Issue 4. Consult with an immunologist regarding the significance of the immune effects observed in Glaser et al. (1985).

The panel reached unanimous consensus that the issue of immunotoxicity was satisfactorily resolved for the purposes of this RfC development. The comments of the immunologist were helpful in interpreting the immune effects observed by Glaser et al. (1985). However, several reviewers felt that the immune system may be of some concern; although the data are not available to answer this question conclusively. The panel noted that the Glaser et al. (1985) study was not designed to detect immune effects and the absence of histopathology precludes conclusions regarding immunotoxicity as a critical effect. The panel agreed that it is accurate to state that the LOAEL for immunotoxicity observed in Glaser et al. (1985) is higher than the LOAEL for lung inflammation. Reviewers discussed the appropriateness of using sensitization/asthma as a critical endpoint, but concluded that the data available for this endpoint are not strong enough to use quantitatively. The LOAEL identified for asthma (from a case study in a single person) could be widely variable in a population because it is not known if the person was sensitive to the effects of hexavalent chromium.

Issue 4 is resolved. No additional work is recommended for this issue.

Issue 5. Determine which deep lung effects should or should not be combined in order to use as basis of critical effect. Acknowledge that both the LDH and lung weight endpoints have weaknesses.

The panel reached unanimous consensus that the endpoints of spleen weight and total immunoglobin should not be used for estimating the RfC because they are not of equal value in describing pulmonary inflammation. The remaining discussion of this issue focused on the appropriateness of choosing the single endpoint that is most sensitive and biologically relevant to lung inflammation as the basis of the RfC, compared with the appropriateness of combining several endpoints that are all related to each other and all indicative of lung inflammation for estimating the RfC.

The reviewers noted that LDH in BALF was the most biologically relevant endpoint because it would not be present unless cells were being damaged. However, there was disagreement on whether this was the most sensitive endpoint and whether it is appropriate to use this endpoint alone as the basis of the RfC. Reviewers noted that when comparing the maximum likelihood estimates for the various endpoints, LDH was the

least sensitive; however when comparing the benchmark doses, LDH was the most sensitive. The reviewers noted that the LDH data were not highly variable. One reviewer suggested that the probable reason for this discrepancy was that the models were designed to fit data that increased monotonically, which does not happen with the LDH data. Therefore, the model did not fit the LDH data as well as it fit the other data. The reviewers agreed that there was not a compelling biological reason to use only the LDH in BALF benchmark dose as the basis of the RfC. Therefore, the panel recommended that the benchmark doses for four endpoints from Glaser et al. (1990) (lung weight, protein in BALF, albumin in BALF, and LDH in BALF) be combined as the basis of the RfC. The panel also recommended that the results of either the polynomial model or the power mean response model be used, but that they should not be combined. Several reviewers recommended that the polynomial model be used; the remaining reviewers had no preference and suggested that ChemRisk choose a model.

Issue 5 is resolved. However, the RfC should be revised so that it is based on the combined benchmark doses of four endpoints indicative of lung inflammation as the critical effect: LDH in BALF, protein in BALF, albumin in BALF, and lung weight. The BMDs for these four endpoints should be combined prior to the estimation of the RfC. ChemRisk should not combine the estimates from the polynomial and the power mean response models to estimate the RfC. More reviewers preferred the polynomial model.

Issue 6. Use the default uncertainty factor of 10 for use of a subchronic study, unless better support for reducing this to three can be provided. The uncertainty factors for intra- and interspecies are appropriate as proposed. An uncertainty factor for database may not be needed, but needs better justification.

The panel did not reach consensus on the appropriate choice of uncertainty factors for development of this RfC. The overall uncertainty factor discussed was either 100 or 300. All reviewers agreed on the use of an uncertainty factor of 3 to account for extrapolation from animals to humans and on the use of an uncertainty factor of 10 to protect sensitive individuals. Several reviewers felt that a full 10 uncertainty factor was needed to account for the uncertainty of extrapolating from a subchronic study; however several other reviewers felt that an uncertainty factor of 3 was adequate. One reviewer felt that a 3 was adequate for the use of subchronic data, but that an additional 3 was needed to address database inadequacies.

The following arguments were discussed in favor of requiring a full 10 uncertainty factor for use subchronic data:

· Data from Glaser et al. (1985) indicate that chromium is still accumulating in the lung at the end of the exposure period.

· Data from Glaser et al. (1990) on LDH and protein in BALF show that there is increasing toxicity with increasing exposure time from 30 to 90 days at the two higher dose groups (200 and 400 ug/cu.m.), and there is no histopathologic data from organs

other than the lungs in this study.

· Although the Glaser 18-month study did not demonstrate fibrosis, it did not look for evidence of progression to more severe inflammation as demonstrated by histiocytosis data.

The following arguments were made to support the adequacy of an uncertainty factor of 3 to account for the use of a subchronic study:

· The 18-month study by Glaser used higher doses and did not demonstrate any evidence of fibrosis or other histopathological damage to lungs.

· A study by Nessel et al. (1995) evaluated several inhalation studies and found that in general the difference between 90-day NOAELs and 2-year NOAELs was only a factor of 2.5.

· Data from Glaser et al. (1990) show that for all endpoints examined there is no increasing toxicity with increasing exposure from 30 to 90 days at the two lower doses (50 and 100 ug/cu.m.).

· The endpoints selected as the basis of the RfC are very sensitive precursors of inflammation; therefore they are only a signal event, not the actual adverse effect.

The panel made several recommendations to help resolve the issue of uncertainty factor.Ffor the reviewers who felt that a total uncertainty factor of 300 was required, the arguments made in the current documentation package do not provide adequate support for an uncertainty factor of 100. The revised document should rely more on the observations of the 18-month study and, in particular, focus on a comparison of those endpoints that were measured in both the 90-day and 18-month studies to determine the potential for progression of toxicity. The revised document should include data, if available, on the accumulation of hexavalent chromium in the lung following exposure to lower doses. Finally the work of Nessel et al. (1995) and perhaps a similar study by Gary Foureman of U.S. EPA, which looked specifically at the lung, can be included in the documentation as supporting evidence for a reduced uncertainty factor.

Issue 6 is not resolved. Reviewers might agree to a total uncertainty factor of 100 if stronger support were provided. This support would have to rest primarily on the Glaser 18-month study and data showing the potential for accumulation of lower doses in the lungs. Studies by Nessel et al. (1995) and Gary Foureman might also provide support.

REFERENCES:

Glaser, U., D. Hochrainer, et al. 1985. Low level chromium (VI) inhalation effects on alveolar macrophages and immune functions in Wistar rats. Arch Toxicol. 57:250-256.

Glaser, U., D. Hochrainer, et al. 1986. Carcinogenicity of sodium dichromate and chromium (VI/III) oxide aerosols inhaled by male Wistar rats. Toxicology. 42:219-232.

Glaser, U., D. Hochrainer, et al. 1990. Investigation of irritating properties of inhaled Cr(VI) with possible influence on its carcinogenic action. In: Environmental Hygiene II. N.a. W.H. Seemayer, ed. New York. p. 239-245.

Nessel, C., S. Lewis, K. Stauber, and J. Adgate. 1995. Subchronic to chronic exposure extrapolation: Toxicological evidence for a reduced uncertainty factor. Human and Ecological Risk Assessment. 1: 516.

Managing Potential Conflicts of Interest
Hexavalent Chromium RfC
(Approved April 16, 1998)

TERA peer reviewers donate their time and talents to this effort. They are selected based upon their expertise and qualifications and are employed by many types of organizations. TERA strives to create a balance of expertise and affiliations. However, individual peer reviewers are representing their own expertise and views, not those of their employer.

TERA requested that each peer reviewer identify potential conflicts of interest related to the review of the hexavalent chromium inhalation reference concentration. Each reviewer signed a statement indicating that he or she does not have a conflict of interest with these chemicals, with the following exceptions noted below. The following statements in reference to the hexavalent chromium review were agreed to by the December 1998 panel and were presented at the beginning of the April 16, 1998 meeting. These statements were agreed to by all.

Stuart Baxter -- Dr. Baxter for the University of Cincinnati. He does not have a specific conflict with this assessment and may participate fully; however, Dr. Baxter was not able to make the conference call.

Robert Benson -- Dr. Benson works for the U.S. Environmental Protection Agency. He does not have a specific conflict with this assessment and may participate fully.

Matthew Bogdanffy -- Dr. Bogdanffy works for DuPont. DuPont has conducted limited DNA-protein crosslink studies on chromium, under contract to ChemRisk, and also produces chromium dioxide magnetic tapes; however, these activities do not pose a conflict with the evaluation of the hexavalent chromium RfC. Dr. Bogdanffy may participate fully in the chromium discussions.

John Christopher - Dr. Christopher is toxicologist with the California Environmental Protection Agency (Cal EPA). Cal EPA regulates various aspects of production, use, sale or disposal of many chemicals, including chromium. However, Dr. Christopher does not have a specific conflict of interest and may participate fully in all discussions.

Gary Diamond -- Dr. Diamond works for Syracuse Research Corporation. Dr. Diamond may participate fully in the chromium discussions.

Michael Dourson - Dr. Dourson is the Director of TERA. TERA has performed work for the City of Kearny, New Jersey which was paid for by Chemical Land Holdings, one of the chromium sponsors, on dermal issues related to exposure to chromium. This work does not create a conflict with the inhalation RfC for hexavalent chromium and therefore, Dr. Dourson may participate fully in the chromium discussions.

Linda Erdreich -- Dr. Erdreich works for Bailey Research. She has no conflicts and may participate fully.

Marvin Friedman - Dr. Friedman formerly worked for CYTEC Industries. Dr. Friedman may participate fully in the chromium discussions; however, he was not able to make the conference call.

Michael Gargas -- Dr. Gargas works for ChemRisk. Dr. Gargas has worked extensively on chromium and for the chromium RfC sponsors. In December 1996 Dr. Gargas was approved to participate in the discussion of the chromium assessment, but not be polled for a recommendation. Dr. Gargas cannot make this conference call.

Andrew Renwick -- Dr. Renwick is on the faculty of the University of Southampton. Dr. Renwick does not have a conflict with the chromium assessment. Dr. Renwick may participate fully in the discussions. Dr. Renwick is not able to make the conference call.

Kenneth Poirier -- Dr. Poirier works for The Procter and Gamble Company. He has no conflicts and may participate fully.