Report of the *ITER* Review Meeting on Literature Risk Values for Chromium VI

August 23, 2012

***ITER* Review Organized by**
Toxicology Excellence for Risk Assessment
(http://www.tera.org/peer)

NOTE

This report was prepared by scientists of TERA and reviewed by the panel members. The members of the panel served as individuals on this panel, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

Table of Contents

Subject Publications and Participants

Chromium VI (CASRN 1344-43-0)

The manuscript by Casey Crump, Kenny Crump, Eric Hack, Rose Luippold, Kenneth Mundt, Elizabeth Liebig, Julie Panko, Dennis Paustenbach, and Deborah Proctor (2003) entitled, "Dose-response and risk-assessment of airborne hexavalent chromium and lung cancer mortality" describes the derivation of cancer potency estimates for chromium VI. The sponsors of this research were Tierra Solutions, Inc., Elementis Chromium, Occidental Chemical Corporation, and PPG Industries.

The review panel members included Dr. Michael Dourson, Toxicology Excellence for Risk Assessment (TERA); Dr. John Reichard, University of Cincinnati; and Dr. John Christopher, Independent Consultant.

Background

The purpose of the International Toxicity Estimates for Risk *(ITER)* database is to provide risk assessors and managers with the latest human health risk values from organizations around the world. *ITER* includes chronic human health risk data from the Agency for Toxic Substances and Disease Registry (ATSDR), Health Canada, International Agency for Research on Cancer (IARC) (in progress), National Institute of Public Health and the Environment (RIVM) - The Netherlands, U.S. Environmental Protection Agency (U.S. EPA), and independent parties whose risk values have undergone peer review. However, the peer reviewed literature contains many more risk values that may be of value to risk practitioners. Therefore, TERA developed a process to include these peer-reviewed, "literature-based," values on the *ITER* database. In order to be considered for inclusion on *ITER*, "literature-based" values must meet the following criteria:

- Manuscript that includes derivation of a risk assessment value has been published in a peer-reviewed journal;
- Assessment follows an identified, commonly used methodology (e.g., U.S. EPA, IPCS, Health Canada); and
- The manuscript's acknowledgment clearly states the source of funding for the work, or the authors provide this source of funding at the review meeting for full disclosure to the panel and on *ITER*.

Authors of peer reviewed publications that meet these criteria submit their publications for an additional quality evaluation by a panel of risk experts. TERA staff screens each publication to determine: (a) if each value was developed using a commonly accepted methodology, and (b) if the resulting risk value is consistent with the types of information *ITER* is designed to include (e.g., chronic human health risk values). The review panel then meets to discuss issues and address the charge questions. The values that the panel deems to be scientifically sound are then loaded on the *ITER* database to make these values more widely available.

Panel Selection and Conflict of Interest Evaluation

TERA has developed an extensive list of expert scientists interested in serving on our peer review panels. For each *ITER* Review meeting, TERA sends an invitation to all potential panelists asking for volunteers willing to participate in the review meeting process on a pro-bono basis. TERA screens the panel volunteers to ensure that the resulting panel includes the necessary expertise to evaluate the risk values under review and to ensure there are no conflict of interest issues. In the instance that there are more volunteers than needed, TERA adjusts the panel membership and insures a proper balance of expertise. When a TERA value is being reviewed, an outside independent party reviews the panel membership and conflict of interest.

An essential part of an independent expert review is the identification of conflicts of interest and biases that would disqualify a candidate, as well as identification and disclosure of situations which may appear to be a conflict or bias. The purpose for evaluating conflict of interest is to ensure that the public and others can have confidence that the peer reviewers do not have financial or other interests that would interfere with their ability to carry out their duties objectively. TERA follows the U.S. National Academy of Sciences (NAS) guidance on selection of panel members to create panels that have a balance of scientific viewpoints on the issues to be discussed. As a result, the expert panels have a broad and diverse range of knowledge, experience, and perspective, including diversity of scientific expertise and affiliation. Panel members serve as *individuals*, representing their own personal scientific opinions. They do not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

For the August 23, 2012 meeting, three experts volunteered to serve on the panel:

- Dr. Michael Dourson, Toxicology Excellence for Risk Assessment (TERA);
- Dr. John Reichard, University of Cincinnati; and
- Dr. John Christopher, Independent Consultant.

TERA asked each candidate to report on his or her financial and other relationships with the authors and sponsors of the risk value by completing a questionnaire. The completed questionnaires were reviewed by TERA staff and discussed further with panel candidates as needed. (See www.tera.org/peer/COI.html for TERA conflict of interest and bias policy and procedures for panelist selection.) TERA determined that the selected panel members have no conflicts of interest and are able to objectively participate in this review. None of the panel members has a financial or other interest that would interfere with his or her abilities to objectively participate on the panel. None of the panel members is employed by the organizations that authored or sponsored the risk values. None of the panel members was involved in the preparation of the risk values.

Meeting Procedure

For the *ITER* Review meetings, the authors provide TERA with a documentation package, including supporting data and analyses, to support their risk value. TERA staff screens each package to ensure completeness. TERA has prepared a standard list of charge questions, which outlines the issues and

questions to guide these reviews (see Appendix A). TERA forwards these charge questions to the panel, and panel members have the opportunity to add to the charge if additional questions are needed. TERA distributes the review materials and charge to panel members prior to the meeting. Panel members are given the opportunity to request additional literature as needed and to submit written pre-meeting comments as necessary.

TERA distributed the review materials and charge to panel members on August 20, 2012.

At the meeting, the author briefly presents the assessment, and then the panel members are given the opportunity to ask clarifying questions. The panel then conducts a thorough, systematic discussion of the key data and decisions using the charge questions. The panel members are asked to indicate whether or not each risk value should be included on *ITER*. Panel members are also asked to note any substantive points or issues to include in the *ITER* file that they think would be helpful for the *ITER* user to be aware of when considering these values.

Panel comments and conclusions for the meeting are described for the manuscript in Appendix B.

Meeting Report

After the meeting, the panel (assisted by a TERA scientist) compiles its recommendations and summarizes them for inclusion on *ITER*. Appendix B provides the summaries of the panel's review comments on the publication that was reviewed on August 23, 2012. This meeting report serves as a record of the review; it has been reviewed by the panel members for accuracy before it is finalized.

Appendix A

Charge Questions for *ITER* Reviews

1) METHODOLOGY

- Was an appropriate risk assessment methodology used and applied correctly? Was the methodology applied correctly, and are the conclusions solid based on the work done? Other comments?

2) ASSESSMENT QUALITY

- Was a literature search done and fully explained/evaluated? Do the authors discuss alternative modes of action, viewpoints, or existing assessments? Other comments?

3) CONCLUSIONS

- Are the publication's conclusions scientifically sound and supported by the data? Do the authors fully explain and support the choice of critical effect, point of departure, and dose-response? Other comments?

4) VALUE

- Is this publication of sufficient value to include on *ITER*? Who are the intended users of the derived value, and how do they benefit from this information on *ITER*? Other comments?

5) OTHER

- Are there additional issues or comments relevant to the publication's risk value and its conclusions?

Appendix B

Hexavalent Chromium (CrVI)

CAS NO: 18540-29-9
ITER PR-August 2012

Source Documents:

Crump, C., Crump, K., Hack, E., Luippold, R., Mundt, K., Liebig, E., Panko, J., Paustenbach, D., Proctor, D.M. (2003). Dose-response and risk-assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 23, 1147-1163.

ToxStrategies, Inc. 2012. *ITER* White Paper –In Support of the Inhalation Cancer Risk Assessment of Hexavalent Chromium. Rancho Santa Margarita, CA.

Data Summary

	Key Information/Data
Chemical Name	Hexavalent chromium
CASRN	18540-29-9
Risk Value	0.00978 $(\mu g/m^3)^{-1}$
Year of Publication	2003
Point of Departure (POD) (Experimental)	NA, based on carcinogenic potency in occupational cohort
POD (Adjusted)	NA
Uncertainty Factors	NA
Target Organ	Lung (cancer)
Species	Human
Study	Crump et al., 2003

Synopsis:

This study evaluates the dose-response relationship for inhalation exposure to hexavalent chromium [Cr(VI)] and lung cancer mortality for workers of a chromate production facility, and provides estimates of the carcinogenic potency. The data were analyzed using relative risk and

additive risk dose-response models implemented with both Poisson and Cox regression. Potential confounding by birth cohort and smoking prevalence were also assessed. Lifetime cumulative exposure and highest monthly exposure were the dose metrics evaluated. The estimated lifetime additional risk of lung cancer mortality associated with 45 years of occupational exposure to 1 $\mu g/m^3$ Cr(VI) (occupational exposure unit risk) was 0.00205 (90%CI: 0.00134, 0.00291) for the relative risk model and 0.00216 (90%CI: 0.00143, 0.00302) for the additive risk model assuming a linear dose-response for cumulative exposure with a 5 year lag. Extrapolating these findings to a continuous (e.g., environmental) exposure scenario yielded an environmental (24 hours per day for a lifetime) unit risk of 0.00978 (90%CI: 0.00640, 0.0138) for the relative risk model [e.g., a cancer slope factor of 34 $(mg/kg\text{-}day)^{-1}$] and 0.0125 (90%CI: 0.00833, 0.0175) for the additive risk model. The relative risk model is preferred because it is more consistent with the expected trend for lung cancer risk with age. Based on statistical tests for exposure-related trend, there was no statistically significant increased lung cancer risk below lifetime cumulative occupational exposures of 1.0 $mg\text{-}yr/m^3$, and no excess risk for workers whose highest average monthly exposure did not exceed the previous Permissible Exposure Limit of 52 $\mu g/m^3$. It is acknowledged that this study had limited power to detect increases at these low exposure levels.

In 2006, OSHA used this study as one of two focus studies for quantitative cancer risk assessment and as justification for changing the Permissible Exposure Limit (PEL) for Cr(VI) from 52 to 5 $\mu g/m^3$ (OSHA 2006), and OSHA and NIOSH occupational unit risk estimates for another cohort of chromate production workers as published by Gibb et al. (2000), yielded results that within a factor of 5 of those calculated here, demonstrating cohesiveness of risk estimates for inhalation exposure to Cr(VI).

For consistency with current cancer risk assessment practice (U.S. EPA 2005), a white paper was prepared to supplement the published mortality, exposure reconstruction and risk assessment studies. The white paper provides a discussion of the carcinogenic mode of action (MOA) underlying Cr(VI)-induced carcinogenicity based on the modified Bradford Hill Criteria, and important toxicokinetic considerations in risk assessment. The weight of evidence supports that Cr(VI)-induced carcinogenicity in the lung acts by a non-mutagenic MOA that involves oxidative stress and oxidative DNA damage, tissue injury and inflammation, occurring at the high exposure concentrations experienced historically in the chromate production industry, and as demonstrated *in vitro* and in animal models. The weight of evidence from current mechanistic data are supportive of non-linearity in the dose-response for lung cancer risk in the low dose range; however the currently available epidemiologic data do not provide sufficient statistical power in the low dose range to quantify non-linearity if it exist.

Overview of Approach

The mortality (through 1997) among 492 former workers of a chromate chemical production plant in Painesville, Ohio, was assessed. Cohort members were employed at least one year between 1940 and 1972 (when the plant closed). Standardized mortality ratios (SMRs) using both U.S. and Ohio reference rates were calculated for selected cause-specific categories of death including lung cancer. Lung cancer mortality was investigated further by calculation of SMRs stratified by year of hire, duration of employment, time since hire, and categories of cumulative

exposure to Cr(VI). SMRs were significantly elevated for all causes combined (SMR=129, 95% CI 115-144), all cancers combined (SMR=155, 95% CI 125-191), and lung cancer (SMR=241, 95% CI 180-317). A trend test showed a strong relationship between lung cancer mortality and cumulative hexavalent exposure (p=0.00002). Lung cancer mortality was elevated for the highest cumulative exposure categories: ≥1.05 to <2.70 mg/m^3-years, SMR=365, 95% CI 208-592; ≥2.70 to <27.80 mg/m^3-years, SMR=463, 95% CI 283-716, but not for the first three exposure groups. Significantly elevated SMRs were also found for year of hire before 1960, 20 or more years of exposed employment, and latency of 20 or more years.

Exposure estimates were reconstructed using a job-exposure matrix (JEM) that related job titles with area monitoring data from 21 industrial hygiene surveys conducted from 1943 to 1971. No personal monitoring data were collected. Specifically, airborne Cr(VI) concentration profiles for 22 areas of the plant were constructed for three distinct time periods (1940–1949, 1950–1964, and 1965–1972), with cut points based on known major plant and process changes. For nearly all jobs, exposures decreased over time, particularly after 1964. For example, average airborne concentrations in production areas of the plant decreased from 0.72 mg/m^3 in the 1940s to 0.27 mg/m^3 from 1950 to 1964, and the average was 0.039 mg/m^3 after 1964. Former workers were interviewed to determine activity patterns in the plant by job title. This information was combined with Cr(VI) monitoring data to calculate cumulative occupational exposure for each worker. Cumulative exposures ranged from 0.003 to 23 (mg/m^3)×years. The highest monthly 8-hour average exposure concentration for each worker ranged from 0.003 to 4.1 mg/m^3.

Exposure estimates were combined with mortality data for this cohort to assess the lung cancer risk associated with inhaled Cr(VI), and a positive dose-response relationship was observed for increases in lung cancer mortality with measures of cumulative exposure and highest monthly exposure.

Quantitative Estimate:

The estimated lifetime additional risk of lung cancer mortality associated with 45 years of occupational exposure to 1 μg/m^3 Cr(VI) (occupational exposure unit risk) was 0.00205 (90%CI: 0.00134, 0.00291) for the relative risk model and 0.00216 (90%CI: 0.00143, 0.00302) for the additive risk model assuming a linear dose-response for cumulative exposure with a 5 year lag. Extrapolating these findings to a continuous (e.g., environmental) exposure scenario yielded an environmental unit risk of 0.00978 (90%CI: 0.00640, 0.0138) for the relative risk model [e.g., a cancer slope factor of 34 (mg/kg-day)$^{-1}$] and 0.0125 (90%CI: 0.00833, 0.0175) for the additive risk model. The inhalation unit risk for continuous exposure, calculated using a 5-year lag and the relative risk model, for the dose metric of cumulative exposure is proposed for inclusion in *ITER*. The value is 0.00978 (μg/m^3)$^{-1}$.

Bibliography:

Crump, C., Crump, K., Hack, E., Luippold, R., Mundt, K., Liebig, E., Panko, J., Paustenbach, D., Proctor, D.M. (2003). Dose-response and risk-assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal 23, 1147-1163.

Luippold, R.S., K.A. Mundt, R.P. Austin, E. Liebig, J. Panko, C. Crump, K. Crump, and D. Proctor. (2003). Lung cancer mortality among chromate production workers. Occup. Environ. Med. 60, 451–457.

Proctor, D.; Panko, J.; Liebig, E.; et al.: (2003). Workplace Airborne Hexavalent Chromium Concentrations for the Painesville, Ohio Chromate Production Plant (1943–1971). Appl Occup Environ Hyg J 18, 430-449.

Proctor, D. M., Panko, J. P., Liebig, E. W., Paustenbach, D. J. (2004). Estimating Historical Occupational Exposure To Airborne Hexavalent Chromium In A Chromate Production Plant: 1940-1971. JOEH 1, 752-767.

ToxStrategies, Inc. 2012. *ITER* White Paper –In Support of the Inhalation Cancer Risk Assessment of Hexavalent Chromium. Rancho Santa Margarita, CA.

Results of Review

Overall assessment:

Based on the reading and analysis of the information provided, the panel identified their overall recommendation for the proposed *ITER* materials they reviewed as:

☑ Acceptable with comments (as indicated)

Panel Conclusions and Recommendations

The panel determined on August 23, 2012 that the risk value derived in "Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality," by Crump et al. (2003) should be included on the *ITER* database, with the recommended revisions to the *ITER* file to include MOA synopsis and white paper summary in *ITER* summary, as well as, link to the white paper. Panel responses to the specific charge questions are provided below.

1) METHODOLOGY

- Was an appropriate risk assessment methodology used and applied correctly? Was the methodology applied correctly, and are the conclusions solid based on the work done? Other comments?

Comments:

All agree that appropriate risk assessment methodology was used and applied correctly and that the white paper should be loaded to *ITER* summary, it adds more mode of action description.

2) ASSESSMENT QUALITY

- Was a literature search done and fully explained/evaluated? Do the authors discuss alternative modes of action, viewpoints, or existing assessments? Other comments?

Comments:

All agreed that the literature has been fully evaluated since the development of the toxicity value and all new relevant information has been addressed in the supporting white paper. These references include discussion of modes of action and existing assessments.

3) CONCLUSIONS

- Are the publication's conclusions scientifically sound and supported by the data? Do the authors fully explain and support the choice of critical effect, point of departure, and dose-response? Other comments?

Comments:

All agreed that the paper has done a good job evaluating data available and the publications conclusion is supported by the data. The paper is clear and explains the support for selection critical effect, point of departure and dose-response and it results in a high confidence in cancer potency.

4) VALUE

- Is this publication of sufficient value to include on *ITER*? Who are the intended users of the derived value, and how do they benefit from this information on *ITER*? Other comments?

Comments:

All agreed that the publication is of sufficient value to be included on *ITER*. It is good to make value available on a government website and it is consistent with previous values. The analysis provided in the publication, along with the white paper shows the current status and data gaps of the inhalation toxicity for hexavalent chromium and provides a starting point for further analysis.

5) OTHER

- Are there additional issues or comments relevant to the publication's risk value and its conclusions?

Comments:

All agreed that a mode of action discussion be written and included in *ITER* file, and would include a link to the white paper. A synopsis of white paper should also be added to summary. All agree value is solid and should be included on *ITER*.

Date: 9/13/2012 (MD); 9/18/2012 (JR); 10/10/12 (JC)
Panel Members: Michael Dourson, John Reichard, John Christopher