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Report of Letter Peer Review of TCEQ's Hexavalent Chromium Section 4.2 Carcinogenic Potential - Development Support Document

Submitted to:

Texas Commission on Environmental Quality (TCEQ)

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Submitted by:
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Note

This report was compiled by scientists of Toxicology Excellence for Risk Assessment (TERA). The peer reviewers served as individuals, 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.

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1. Introduction

This report summarizes external peer review comments on Section 4.2 Carcinogenic Potential of the Development Support Document for Hexavalent Chromium. Toxicology Excellence for Risk Assessment (TERA) organized and conducted an independent external scientific and technical peer review of this document for the Texas Commission on Environmental Quality (TCEQ). The goal of the peer review was to have a group of qualified external experts conduct a thorough and meaningful assessment of the document and provide an independent evaluation of the robustness of the science and whether the conclusions are supported by the body of evidence.

The Toxicology Division of the Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that outlines the hazard assessment and dose-response processes used to derive health-protective Effects Screening Levels (ESLs) and Reference Values (ReV) for hexavalent chromium (CrVI). The draft DSD includes Section 4.2, which documents the derivation of an inhalation unit risk factor (URF) and air concentrations corresponding to the policy-based 1 in 100,000 excess risk level based on lung cancer mortality. These toxicity values are used in the evaluation of air permit applications and ambient air data and were developed using RG-442 TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). The TCEQ guidelines can be found at http://www.tceq.texas.gov/publications/rg/rg-442.html.

1.1 Peer Review Organization

TERA was responsible for managing all aspects of the peer review process, including selection of the reviewers, evaluation of potential conflicts of interest of candidate reviewers, development of the charge questions, distribution of the assessment document, collection and review of each expert's written comments, and compilation of all comments into a single report (this report).

Alliance for Risk Assessment (ARA) –This peer review is a project under the Alliance for Risk Assessment (ARA). ARA is a collaboration of organizations that fosters the development of technical chemical risk assessment products and services, through a team effort of specialists and organizations dedicated to protecting public health by improving the process and efficiency of risk assessment, and to increasing the capacity for developing risk values to meet growing demand. All ARA projects are vetted by a Steering Committee comprised of federal and state government, academic, and NGO perspectives, to promote scientific relevance and avoid duplication of effort. As an ARA project, this project was led by an independent, nonprofit organization, performed in an open and transparent manner, and the results will be made publicly available at www.allianceforrisk.org .

Selection of Reviewers. TERA reviewed the draft document and in consultation with TCEQ identified the types of expertise needed for the peer review. These included familiarity with hexavalent chromium toxicology and epidemiology literature, quantitative epidemiology, exposure response modelling, biostatistics/biomathematics, toxicology, and cancer risk assessment. TERA developed a list of potential experts that TERA judged to be qualified. This list was shared with TCEQ in order for the scientific authority to identify any reviewers who may have a potential conflict of interest or those who they thought unqualified. From the final

cleared list, TERA independently selected four reviewers who collectively covered the needed areas of expertise to provide a high-quality peer review of the assessment.

TERA discussed the situations and conditions that may be considered potential conflicts of interest (COI) for the peer reviewers with TCEQ, and developed a COI questionnaire to screen all candidates. TERA's conflict of interest policy is found at http://www.tera.org/peer/COI.html. After reviewing credentials and COI information, TERA selected a group of reviewers that provide a balance of appropriate expertise and perspectives for this peer review. To maintain the independence of the peer review, the experts have had no direct contact with TCEQ. The expert peer reviewers for this assessment are listed below. Their affiliations are provided for identification purposes only. Appendix A contains short biographical sketches of the experts and results of the conflict of interest screening.

- David Gaylor, Ph.D. – Private consultant, Gaylor and Associates, LLC, Eureka Springs, AR, USA
- Kyle Steenland, Ph.D. – Professor of Environmental/occupational Epidemiology, Environmental Health Department at the Rollins School of Health, Emory University, Atlanta, GA, USA
- M.E. (Bette) Meek, Ph.D. – Associate Director of Chemical Risk Assessment at the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, ON, Canada
- Michael Dourson, Ph.D., DABT – President of Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH, USA

Development of Charge. A key aspect of a successful peer review is a comprehensive list of objective questions to frame the reviewers' comments and ensure that the reviewers are focused on the most important issues. TERA drafted a list of questions and issues for this "charge" to the peer reviewers and sent a draft of the charge to TCEQ for comment and input. TERA, as the independent organizer of the peer review, considered TCEQ's input on the charge questions, but was responsible for the final content and wording of the charge. The charge questions focus on the adequacy, quality and relevance of the data and information and whether the conclusions reached are supported by the data. Focused and open-ended questions were used to provide reviewers with the opportunity to identify and discuss all the issues they felt were important. A copy of the charge and instructions for reviewers is found in Appendix B.

Reviewers' Comments. Reviewers were allotted several weeks to review the draft document and submit comments to TERA. TERA compiled reviewers' comments by charge question, randomly assigning each reviewer a number that was used throughout the report. The assigned reviewer number is meant to keep each reviewer's specific comments anonymous, although the names and affiliations of the reviewers are provided. TERA staff screened the experts' comments for completeness and clarity, and TCEQ was given the opportunity to review the peer reviewers' comments and submit to TERA clarifying questions for the reviewers.

Request for Public Comments. TERA posted information about the peer review on a publically-accessible web page and provided the opportunity for members of the public to submit comments. Two public comments were received and have been included in this report (see Appendix B).

The experts' comments were compiled into this comprehensive report entitled, *Report of Letter Peer Review of TCEQ's Hexavalent Chromium - Section 4.2 Carcinogenic Potential - Development Support Document.* TCEQ reviewed the draft peer review report and had no clarifying questions for the reviewers.

2. Peer Reviewer Responses General Questions

2.1 Does the draft DSD clearly describe the approaches used by TCEQ to develop the URF? (Charge Question 1)

2.1.1 Reviewer 1

Yes, especially the derivation of the slope factor (beta) relating cumulative chromium VI to lung cancer from two key studies. If anything could use more transparency, it would be the final steps of deriving the URF and the ESL. Although the steps to arrive at these numbers are outlined in methods, some further description of their derivation could be given in the section (p. 27) where the final numbers are presented.

2.1.2 Reviewer 2

The draft DSD clearly and extensively describes the approaches used by the TCEQ to develop the unit risk factor (URF). Section 3.1.2 provides a good review of the mode of action (MOA) for Chromium VI. Section 4.2.1 provides a good review of the weight of evidence for the selection of lung cancer as the primary toxicological effect. Section 4.2.2 provides a good discussion of the carcinogenic MOA. Section 4.2.3 it is appropriately stated on page 8 that default liner low-dose extrapolation is utilized for the cancer dose response. The choice of cumulative exposure is justified. The selection of epidemiological studies and choice of dose response regression models are adequately discussed. The duration of exposure, lagged exposure, and covariates such as smoking are appropriately considered. An adjustment of dose from occupational exposure to continuous exposure to chromium VI is appropriately applied. Texas background cancer rates were used to appropriately calculate standard mortality ratios. A weighted estimate of two URFs was correctly employed for the final URF estimate.

2.1.3 Reviewer 3

The approaches are described very clearly. The document is well-focused, succinct and informative, clearly outlining the considerations on which judgments were based, within the confines of the procedures outlined in the *TCEQ Guidelines to Develop Toxicity Factors.* It appears to have been prepared by an experienced team who is to be congratulated on the transparency with which they have presented their analysis. It also seems to draw meaningfully on previous assessments, as a basis to increase efficiency.

I would only suggest that consideration be given to adding a description of the process for preparation and review to date and basis for the specific focus of this assessment up front. This would provide even greater transparency on aspects of evaluation relevant for review and permit perhaps, even greater focus on critical components thereby additionally increasing efficiency. While this is generally addressed in the *TCEQ Guidelines to Develop Toxicity Factors,* additional information which is currently

lacking includes a priori criteria for determining the extent of reliance on previous assessments versus the nature of, timeframe for and extent of consideration of primary data – e.g., standard searching of identified electronic sources for recent data with criteria specified and cut-off date past which no additional data were considered (What were a priori exclusion criteria for particular studies – e.g., unpublished; published after a certain date?).

2.1.4 Reviewer 4

The draft is very clear in its description of the various epidemiology studies, and in its recommendation to conduct a novel quantitative analysis in the development of the chosen URF. I was particularly gratified to see TCEQ lead this analysis with a discussion on the potential Modes of Action (MOAs). The conclusions of this MOA section seem reasonable to me.

Rather than agree with TCEQ's chosen approach to develop the URF, I suggest an alternative to consider (see response to question 6 below). Several places are noted in the text where the concepts might be further clarified (see attached annotated text).

2.2 Were procedures outlined in RG-442 *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) followed by the TCEQ in this assessment? (Charge Question 2)

2.2.1 Reviewer 1

It's hard to know for sure, as the guidelines are over 200 pages. However, with a brief look at them, it seems that that the TCEQ has followed the guidelines.

2.2.2 Reviewer 2

As described above in the response to Question 1, the options and issues outlined in *RG-442 TCEQ Guidelines to Develop Toxicity Factors* were followed in the draft DSD.

2.2.3 Reviewer 3

It appears that the procedures outlined in RG-442 *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) were appropriately followed, to the extent reasonable. However, such guidelines necessarily provide only a very broad framework, representing a "snapshot in time" in the evolution of methodology, given the extensive workload associated with updates. As a result, individual assessments necessarily incorporate recent developments in methodology. For example, it is noted that while the TCEQ Guidelines were developed very recently, they rely heavily on, for example, the US EPA (2005) Cancer Guidelines. And while the TCEQ Guidelines capture well, I believe, a reasoned interpretation of the intent of the 2005 Guidelines for application, knowledge of and experience in weight of evidence analysis for mode of action has progressed considerably in the interim, particularly in the context of more explicit delineation of the appropriate nature of key events and more consistent and explicit application of the

Bradford Hill considerations for assessing comparative weight of evidence for alternative hypotheses (See comments below).

For example, templates for consideration of the relative degree of confidence that a specific MOA is potentially operative and quantitative impact on inter- and intra-species differences in dose response are included in a recent update to the WHO MOA framework – Meek et al., which has been submitted for publication in Toxicology and Applied Pharmacology. The need to more robustly take into consideration the pattern of results in *in vitro* and *in vivo* genotoxicity assays in assessing potential for a chemical acting by a mutagenic mode of action considering not only the phylogenetic order of the organism and nature of the endpoint but also dose-response in the assays is also recognized (See comments below).

In addition, there are limitations of the MOA analysis which serves as the stated basis for considering in this specific case, that "the available scientific data relevant to the carcinogenic MOA for CrVI are interpreted as adequate to support considering nonlinear-threshold assessments for inhalation carcinogenicity for comparison to default linear low-dose extrapolation approaches."

2.2.4 Reviewer 4

I believe so.

2.3 Please identify any relevant studies or data that have not been cited and would affect an important part of the assessment and explain how they would impact the assessment specifically. (Charge Question 3)

2.3.1 Reviewer 1

I don't think there are any relevant studies not cited. However, I would be curious how this risk assessment coincides or differs from the OSHA 2006 risk assessment which led to a lowering to the occupational standard from 52 to 5 $\mu g/m^3$.

2.3.2 Reviewer 2

Not aware of additional relevant studies or other important data.

2.3.3 Reviewer 3

There is a series of articles, both published and in press, which additionally articulate principles and robust approaches for mode of action analysis, building on considerable evolving experience internationally. These include the following:

- Seed et al. (2005) Crit Rev Toxicol 35: 663
- Boobis et al. (2006) Crit Rev Toxicol 36:781
- Boobis et al. (2008) Crit Rev Toxicol 38:87

- Meek (2008) Env Mol Mutagenesis 49:(2) 110
- Meek & Klaunig (2010) Chemico-Biological Interactions 184:279–285
- Meek et al. (submitted) Toxicol. Appl. Pharmacol.

While not part of the assessment, specifically, this experience has implications for the analysis included in the Haney et al. (2012) paper which serves as the reference for the statement in the assessment (page 7, last paragraph) "wherein available scientific data relevant to the carcinogenic MOA for CrVI are interpreted as adequate to support considering nonlinear-threshold assessments for inhalation carcinogenicity for comparison to default linear low-dose extrapolation approaches." In my view, while the content of the paper is interesting from the perspective of hypothesis generation, the mode of action analysis included therein does not constitute adequate basis in itself to support considering non-linear threshold assessments (see additional comments below). While this observation is not at odds with the critical conclusion to rely on linear extrapolation, it has implications also for the rationale by which this conclusion was reached.

(page 8, first paragraph):

"However, while data relevant to the carcinogenic MOA and the epidemiological analyses conducted support consideration of nonlinear-threshold assessments for CrVI inhalation carcinogenicity, the uncertainties associated with the assessment (e.g., limited statistical power of epidemiological studies to detect increased risk at low exposure levels, lack of a statistically better fitting threshold model, lack of data on competing rates of extracellular CrVI reduction and lung tissue absorption) appear to preclude a robust scientific justification for deviation from the default linear low-dose extrapolation approach. Thus, the nonlinear-threshold assessment is not a focus of this document and the default linear low-dose extrapolation approach is utilized in the following sections to derive URF estimates based on various epidemiological studies."

2.3.4 Reviewer 4

I am not aware of additional studies that could be cited other than the draft IRIS assessment for chromium of the U.S. Environmental Protection Agency (EPA). However, I understand why TCEQ might not wish to refer to this EPA text since it is in review, especially since EPA asks for it not to be cited or quoted.

3. Peer Reviewer Responses to Questions on Cancer Assessment and Unit Risk Factor (URF)

3.1 Section 4.2.1 presents carcinogenic weight of evidence classification information and conclusions of authoritative bodies. Is TCEQ's weight of evidence conclusion appropriate? If not, what alternative conclusion is appropriate and why? Is the decision to apply the URF to all forms of CrVI appropriate for public health protection purposes? (Charge Question 4)

3.1.1 Reviewer 1

I believe the weight of the evidence conclusion appropriate. I also agree that lumping all forms of CrVI together is appropriate given the epidemiology, which essentially does the same.

3.1.2 Reviewer 2

The carcinogenic weight of evidence presented by the TCEQ in the DSD is scientifically appropriate, supported by authoritative bodies, and follows the TCEQ RG-422 guidelines. The decision to apply the URF to all forms of CrVI appears most appropriate for public health protection.

3.1.3 Reviewer 3

TCEQ's weight of evidence conclusion seems appropriate and consistent with those of other authoritative bodies. The assessment has, then, reasonably drawn upon the conclusions of others in providing adequate documentation for the purpose at hand. The additionally informative narrative descriptors concerning route and dose under which cancer is likely to result are also helpful as a basis to increase understanding of the classification. In the absence of presentation or consideration of information relevant to distinction of various forms of CRVI in this context, the decision to apply the URF is conservative, and is consistent with public health protection policy.

3.1.4 Reviewer 4

TCEQ's weight of evidence conclusion, that "TCEQ considers CrVI and CrVI compounds as a group to be carcinogenic to humans via inhalation (at least at sufficiently high long-term doses)" is appropriate based on its analysis, and on the analysis of other expert bodies. This conclusion is consistent with TCEQ's evaluation of the possible MOAs of chromium's tumorigenicity and its guidelines. The choice to consider all CrVI forms as carcinogenic also appears to be scientifically appropriate based on TCEQ's MOA discussion.

One apparent inconsistency in TCEQ's text is that the ability of the CrVI form to cross a cell membrane is paramount to the MOA conclusions, but that "particulate forms of CrVI, relatively water insoluble compounds more specifically (e.g., moderate to low

solubility), appear to be more potent lung carcinogens." [TCEQ text page 4] This also occurs with inhaled nickel compounds, due to the fact that moderate-to-low soluble forms of nickel stay in the lung longer and result in more intracellular nickel---in this case, more soluble nickel forms are more readily excreted, or absorbed systemically, resulting in less intracellular-lung nickel [see, for example, Goodman et al. 2011]. TCEQ may wish to discuss this for chromium compounds as well or at least reference the nickel discussion.

3.2 Section 4.2.2 discusses hexavalent chromium's carcinogenic mode of action (MOA). Have the authors clearly and accurately summarized the proposed hypotheses for the MOA, given the current state of knowledge? (NOTE: Please keep in mind that the purpose of the DSD is to document the derivation of the URF and ESL as opposed to being a comprehensive weight of evidence paper on the MOA. Therefore, if data on the MOA are not sufficient to justify an alternate approach to linear low-dose extrapolation, the DSD only needs to generally summarize the primary proposed MOAs, MOA issues, and justify use of the default extrapolation method [see next question]. (Charge Question 5)

3.2.1 Reviewer 1

I think the presentation of the MOA is appropriate and limited interferences from it are also appropriate. There is not sufficient evidence to justify an alternative to the linear low-dose extrapolation.

3.2.2 Reviewer 2

The DSD clearly and accurately summarizes the proposed hypotheses for the Mode of Action (MOA) of CrVI. The DSD correctly concludes that sufficient information on the MOA is not available to justify deviation from default linear low-dose extrapolation.

3.2.3 Reviewer 3

It's appropriately noted in Section 4.2.2 that "a thorough discussion of the MOA evaluations conducted to date are (sic) beyond the scope of this document" and readers are referred "to the cited references and scientific literature for detailed information".

In addition, it is indicated that "there should be a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA and the TCEQ believes such a standard has not been met for CrVI (i.e., merely demonstrating plausibility is not tantamount to an adequately robust demonstration that mutagenicity is in fact THE initiating event in target tissues) ".

Taking into account the first qualification above which transparently indicates the bounds of appropriate investment in considering mode of action for the purpose at hand, I believe that TCEQ has presented a clear summary of the hypothesized modes of action, based on available data. What is not presented, currently, is a meaningful analysis of the

extent of experimental support for the various hypothesized modes of action based on robust analysis of comparative weight of evidence as a basis for justification that "the available scientific data relevant to the carcinogenic MOA for CrVI are interpreted as adequate to support considering nonlinear-threshold assessments for inhalation carcinogenicity for comparison to default linear low-dose extrapolation approaches". The latter is not, in my view, adequately supported on the basis of the content of the Haney et al. (2012) paper, based on the rationale provided below.

It is assumed in the Haney et al. (2012) paper and summarized in the TCEQ assessment that: "While the proposed MOAs differ, what they have in common as the earliest key events is an assumption (inherent or explicitly stated) that CrVI has escaped extracellular reduction to enter cells of the target tissue, followed by the intracellular reduction of CrVI. Experimental data support the reduction of CrVI to CrIII as an important detoxification mechanism, which may represent a hurdle to CrVI-induced carcinogenicity in some instances (e.g., low exposure well within lung CrVI reductive capacity extracellular to target tissue)."

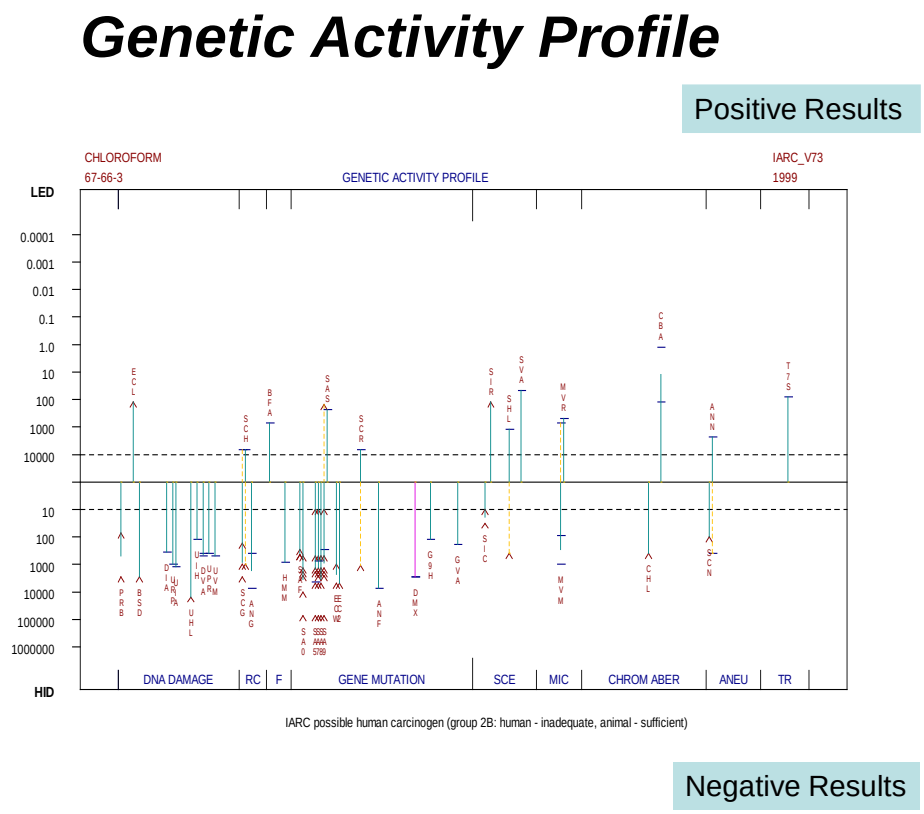
The assumption presented above appears to be predicated on a misunderstanding of the nature of key events as defined based on the EPA (2005) Cancer Guidelines in the TCEQ guidance and the relevant roles of consideration of kinetics and dynamics in scaling of dose-response assessment in mode of action/human relevance analysis. While metabolism to the toxic entity (considered part of dynamics) is often an important early key event, absorption, distribution and excretion (and factors which influence same) are not normally considered in this context. Rather, such aspects are addressed as critical components of the quantitative concordance analysis. For example, if conversion to the toxic entity is considered a critical determinant of interspecies differences or human variability, this is addressed in quantitative scaling between species and within humans.

It is inappropriate, in my view, then, to propose that the available data on the required reduction of CrVI to CrIII constitutes adequate basis to justify considering nonlinear-threshold assessments for inhalation carcinogenicity for comparison to default linear low-dose extrapolation approaches for chromium VI. This is not to say that more robust analyses of the weight of evidence of supporting data might justify this approach but rather, that the exploratory analyses included in Haney et al. (2012) is only sufficient, in my view, to provide bounding of quantitative estimates of risk based on epidemiological studies or as a basis to recommend an appropriate strategy for additional investigation to more meaningfully quantitatively-informed estimates of risk.

In addition, there is no indication of the nature of conducted analyses (within available reviews, for example) in which weight of evidence for a mutagenic mode of action has been considered to understand the basis for the conclusion that "the TCEQ believes such a standard has not been met for CrVI (i.e., merely demonstrating plausibility is not tantamount to an adequately robust demonstration that mutagenicity is in fact THE initiating event in target tissues)." This necessarily requires additional analysis of the cited references. My own recollection of the McCarroll et al. (2009) reference is that the

evidence for a potentially mutagenic mode of action may not have been adequately considered (in my view), taking into account, for example, dose-response for the relevant genotoxicity assays.

In this context, additional insight can often be gained from considering the pattern of results in relation not only to level of biological organization but dose response. Such results can be presented graphically as per genetic activity profiles (example below; there is likely one available for Cr VI) and increases understanding of the expectation of different types of genetic damage (including mutation) which may be completely consistent with a hypothesized nonmutagenic mode of action.



Note that the lengths of the lines for positive results (above the line) represent the lowest effective dose for positive results; those for negative results represent the lowest ineffective dose.

3.2.4 Reviewer 4

TCEQ's discussion of carcinogenic MOA is well done. Based on this discussion, TCEQ's conclusions regarding the MOA are well wrought, specifically that:

- The bioavailability and carcinogenic/toxic potential of Cr compounds depend upon the oxidative state? and thus solubility of the Cr atom,

- CrVI carcinogenicity/toxicity appears to be mediated through reactive intermediates, and
- The human body has a significant ability to reduce CrVI to CrIII, extracellular to target tissue as well as intracellularly.

I was somewhat disappointed to then read later in the document that TCEQ was going to conduct a dose response assessment for chromium's carcinogenicity in a linear fashion, presumably since "the scientific community has not reached a consensus on the specific MOA(s) for CrVI-induced lung carcinogenesis, or the role lung reductive capacity may play at low, environmentally-relevant concentrations in terms of risk (e.g., nonlinearity)." [TCEQ page 7]. This choice of linear assessment does not appear to be consistent with TCEQ's MOA discussion, and is not consistent with TCEQ's weight of evidence statement shown in question 4 above, "carcinogenic to humans via inhalation (at least at sufficiently high long-term doses)." Because otherwise, if TCEQ believed that the carcinogenic response was linear to the low dose, why would it need to specify "at least at sufficiently high long-term dose?"

I propose an alternative approach as described in response to question 6 below.

3.3 In Section 4.2.3 TCEQ provides a rationale for not using a nonlinear-threshold dose response approach; do you agree with TCEQ's conclusion that there is not adequate scientific justification to deviate from use of the default linear low-dose extrapolation approach given the inherent uncertainties of available data? (Charge Question 6)

3.3.1 Reviewer 1

I agree. Park and Stayner (2006) make this clear as well, and Crump (2003) recognizes the low power of any effort to define a threshold.

3.3.2 Reviewer 2

Given the inherent uncertainties of available data and information, as stated in the DSD there is not adequate scientific justification to deviate from use of the default linear low-dose extrapolation.

3.3.3 Reviewer 3

I agree that there is not adequate scientific justification to deviate from the use of the default low-dose extrapolation approach not only due to the inherent uncertainties of available data, but to the limitations of the analyses, currently, of mode of action (See other responses). In this context, I'm wondering if the Haney et al. analysis might be best referenced in the context of exploratory analysis to "bound" uncertainty associated with the low dose risk estimates.

3.3.4 Reviewer 4

The two reasons stated for not deviating from the default linear approach on the top of page 8 are labored. The first reason that uncertainties are associated with this assessment, are true of any assessment; epidemiological studies and studies in experimental animals always have limited statistical power to detect increased risk at low exposure levels. Thus, this reason cannot be used as a justification for a default position. One would need to evaluate whether or not these uncertainties are understandable within the MOA framework discussed by TCEQ. Moreover, the second reason, specifically the lack of data on competing rates of extracellular CrVI reduction and lung tissue absorption, is another weak argument. One could equally ask for the receipt of data to justify the linear default, which would then allow a judgment based on a comparison of relative uncertainties. Perhaps TCEQ should describe data to support or refute for a linear and its suggested non-linear MOA.

Although we are reluctant to agree with the authors' use of a linear low-dose approach, TCEQ might consider, or at least describe, an alternative approach. Specifically, a mode of action (MOA) is possible that is linear at low dose reflecting a hypothesized mutagenic key event, but also reflects a regenerative hyperplasia at the higher doses due to a second key event related to cellular damage from oxygen radicals as described by TCEQ in its MOA section. Careful consideration of the information on mutagenic potential taking into account dose-response would help inform the development of the possible mode of action. In fact, EPA's cancer guidelines (2005, page 3-22) supports this kind of approach and Dourson et al. (2008) give an example with acrylamide. Alternatively, it might be that TCEQ's choice of existing models could reflect a dual MOA, but if so, then TCEQ should consider describing their modeling results in this fashion.

3.4 Please comment on the following key decisions in the TCEQ assessment. For each, please discuss if the conclusions and choices are supported by the available data and discuss any additional information, data, or analyses that could improve the decision. (Charge Question 7)

3.4.1 Do you agree that lung cancer mortality is the best cancer endpoint for this dose-response assessment? Are lung cancer incidence and mortality sufficiently similar as to be comparable for purposes of this assessment for the reasons discussed in the DSD?

3.4.1.1 Reviewer 1

Yes incidence and mortality are essentially equivalent for lung cancer.

3.4.1.2 Reviewer 2

For the available data, lung cancer mortality appears to be the best choice for a dose response assessment. As discussed in the DSD and shown in Figure 3, lung

cancer incidence and mortality are sufficiently similar to be nearly comparable for the purposes of this risk assessment.

3.4.1.3 Reviewer 3

I agree that lung cancer mortality is the best cancer endpoint for this dose-response assessment and well substantiated as the critical effect in a large number of assessments, including several that have been conducted relatively recently. The similarity between lung cancer incidence and mortality (Figure 3) is sufficiently similar as to be comparable for purposes of the assessment; analyses of likely limited available data on lung cancer incidence in study cohorts would provide limited opportunity to consider various aspects of causality and dose-response.

3.4.1.4 Reviewer 4

Yes, lung cancer mortality is the best cancer endpoint for this assessment. Lung cancer incidence would be a better endpoint (if it were available) because it also captures those few persons who develop lung cancer and survive, but the currently available data preclude its use. Lung cancer also appears to be the most sensitive of the respiratory cancer endpoints, as TCEQ has stated, based on the information provided in Table 1 of Crump et al. (2003). Although the reported SMR for other respiratory system cancers is much higher (941 versus 241, using Ohio reference rates), their prevalence is extremely low, indicating that they occur rarely and may not be appropriate for consideration.

Lung cancer mortality is predictive of incidence for lung cancer (as shown in Figure 3).

3.4.2 Cumulative CrVI exposure (mg CrVI/m^3-yr) was chosen as the dose metric.

3.4.2.1 Reviewer 1

Cumulative exposure is the appropriate metric for most chronic diseases, including cancer. Some explanation in the text could be presented about the relationship between CrO_3 (used in Park et al. 2004, and in the present text) and CrVI. It is not until the appendix that we learn more about this. At one point in the text a slope factor from the Park et al. is presented in terms of CrVI which is mysterious, as the results from Park et al. are all in units of CrO_3.

3.4.2.2 Reviewer 2

From the available data on exposure, cumulative CrVI exposure (mg CrVI/m^3-yr) appears to be the best dose metric.

3.4.2.3 Reviewer 3

The rationale provided in this context relates principally to it being the only common measure available from the key studies, but also, because cumulative

exposure is the dose metric used for dose-response modeling based on epidemiological studies. It's also noted that information on target tissue in the lung (a much preferred metric) is not available.

I wondered if any thought had been given to doing any sub-analyses based on exposure concentration given that effects in the lung (particularly those associated with particulate matter) are often concentration-related.

3.4.2.4 Reviewer 4

This exposure metric is appropriate.

3.4.3 Were the most appropriate human epidemiological studies (Painesville Ohio and Baltimore Maryland cohorts; Crump et al. [2003] and Gibb et al. [2000]) selected for the dose-response assessment and was their selection sufficiently described and justified? Are there any other published epidemiological studies of inhaled hexavalent chromium exposures with sufficient data that should and could have been considered by TCEQ in deriving the URF?

3.4.3.1 Reviewer 1

Clearly these two cohorts are the key ones for risk assessment. There are no other epidemiologic studies, apart from the supportive 4 low exposure cohorts, of which I am aware. The approach of re-analysis of the Baltimore cohort data, restricted to those with 1+ years of employment, is reasonable. It is comforting that results from this analysis do not differ much from the entire Baltimore cohort.

3.4.3.2 Reviewer 2

Two human epidemiological studies were selected for the dose-response assessment in the DSD (Painesville, Ohio, Crump et al., 2003 and Baltimore, Maryland, Gibb et al., 2000). The choice of the selection of these two studies was sufficiently described and justified in the DSD. No other studies appear to be justified for the derivation of the URF.

3.4.3.3 Reviewer 3

Based on the rationale provided in the DSD (relatively large with most extensive follow up and historical CrVI levels), these appear to be the most appropriate human epidemiological studies for dose-response assessment. Additional analyses for the supporting cohorts contribute additionally to the defensibility of focus on those specified above.

3.4.3.4 Reviewer 4

The Painesville and Baltimore cohorts are the best for use in a dose-response assessment due to their large sample sizes, extensive follow-up, and detailed exposure estimates. I am not aware of any other epidemiological studies that

would be more appropriate. I have some concerns regarding the Baltimore data, specifically due to extremely high percentage of employees who worked for less than one year. Although removal of these workers from the analysis reduces the potential for bias due to an unhealthy lifestyle (and is ultimately necessary for this analysis), there is the risk of introducing selection bias, especially since over 40% of the original population is not considered in the analysis. I also find it interesting that there is not much difference in slope estimates based on the data including only workers with > 0.5 years of employment and >1 year of employment (Table 7).

Ultimately, for the purposes of this assessment and the meta-approach used in the final URF derivation, it is best to use only workers exposed for a year or more, which is also part of the selection criteria for Crump et al. (2003). Thus, I agree with the TCEQ approach.

3.4.4 Were the data from supporting cohorts (Leverrkusen and Uerdingen, Germany; Corpus Christi, Texas; and Castle Hayne, North Carolina) and Applied Epidemiology (2002) used appropriately? Additionally, were the reasons for excluding the URF based on the data from these supporting cohorts (Leverrkusen and Uerdingen, Germany; Corpus Christi, Texas; and Castle Hayne, North Carolina) and Applied Epidemiology (2002) appropriate and sufficiently described?

3.4.4.1 Reviewer 1

Yes, the data were used appropriately. The four low exposure cohorts supply supplemental, but not key information. Their exclusion from the URF calculation is appropriate given the lesser follow-up time for these 4 low exposure cohorts.

3.4.4.2 Reviewer 2

Data from the four supporting cohorts are adequately described in Section 4.2.3. These studies support the presence of a dose response relationship between lung cancer and CrVI exposure in the low-dose region. Because of the shorter follow-up times, numerical estimates of the URF from these studies appropriately were excluded.

3.4.4.3 Reviewer 3

The additional analyses for the low dose cohorts are helpful in characterizing risks in the range of interest with relevant limitations being appropriately described and taken into account. Consistent with the response for part c) above, focus on the critical epidemiological studies mentioned there based on articulated considerations seems appropriate.

3.4.4.4 Reviewer 4

Yes, these data were used appropriately as supporting evidence. Due to the relatively short follow-up period, these data should not be considered as primary studies.

3.4.5 Were the statistical and modeling approaches used to calculate the slope (β) estimates (Section 4.2.3.1.4) and URFs (Section 4.2.3.1.6) for the selected data sets appropriate?

3.4.5.1 Reviewer 1

Yes, the modeling approaches were appropriate. One thing that need to be made clear (assuming I am right here) is that in the Cox regression analyses of the Baltimore data an excess RR model was used. This is not made explicit in the document. Most standard Cox models use a log-linear model, not an ERR model. I would like to know the software used for Cox ERR models. Was this Epicure? This can be done in SAS via PROC NLP (Langholz and Richardson 2010).

3.4.5.2 Reviewer 2

Poisson Regression Modeling and Cox Proportional Hazards Modeling are described in Section 4.2.3.1.4. These two statistical models are appropriate and commonly used to estimate the slope (β) for epidemiological data. Calculation of the Unit Risk Factors (URFs) are correctly described in Section 4.2.3.1.6.

3.4.5.3 Reviewer 3

While this is not my area of expertise, rationales for choice of the statistical and modeling approaches used to calculate the slope estimates and URFs appear to be based on a thoughtful and well-articulated consideration of a range of relevant factors.

3.4.5.4 Reviewer 4

The modeling approaches were appropriate. Although I am not familiar with Cox proportional hazards modeling, it seemed to be a sophisticated approach to dealing with multiplicative risk factors associated with lung cancer mortality.

I understand that this approach was used to mitigate some of the uncertainties associated with the Baltimore cohort, but could it also be utilized for the Crump et al. (2003) cohort? I assume that this approach is not possible due to the lack of availability of the individual exposure estimates and cofactor information, but TCEQ should state why they did not use this approach with this cohort, especially since they state that "Cox modeling is superior than Poisson regression modeling…"

3.4.6 Is use of the central estimate of the URFs sufficiently discussed and justified?

3.4.6.1 Reviewer 1

Yes.

3.4.6.2 Reviewer 2

The central estimate of the slope parameter is discussed sufficiently in Sec. 4.2.3.1.4 for the Poisson regression model and the Cox proportional hazards model. These models are used to estimate the CrVI concentration corresponding to a lung cancer risk of 10% (EC_{10}). The lower confidence limit (LEC_{10}) is calculated to account for inherent variation in the concentration-response data in the epidemiology studies. Calculation of the URF = 0.10 / LEC_{10} as shown on page 20 for low dose linear extrapolation is sufficiently justified.

3.4.6.3 Reviewer 3

I wondered if factors other than those mentioned (i.e., where the number of responses – i.e., observed and expected cases is known) as a basis for justification of use of the central estimates should be considered.

The potential appropriate use of central estimates versus those at lower confidence intervals should, in my view, be considered in all cases, rather than relying on recommended defaults, taking into account a number of other factors including the nature of the estimates of exposure with which hazard levels are likely to be compared (depending on the problem formulation), the stability of the data on which the central estimates are based and the desired degree of conservatism, based on the purpose of the assessment.

3.4.6.4 Reviewer 4

Yes. The use of the central estimate is commonly done in other dose response assessments where human data form the basis of the assessment. This is because the uncertainty in the extrapolation of experimental animal data to humans is avoided, and the added conservatism through the use of the upper bound is not needed.

3.4.7 Are the most appropriate URFs from each study used to calculate the final URF? That is, was the choice of URFs for decision making the best choice – properly adjusted for covariates, based on the optimal exposure lag, and based on the inclusion of workers with a minimum length of employment?

3.4.7.1 Reviewer 1

I would just use the 5 year lag in the Baltimore data. The difference between the optimal lag (7 some years vs. 5 years) for the Baltimore data is imperceptible. For consistency with Crump et al., I would use the 5 years lag.

3.4.7.2 Reviewer 2

The most appropriate URF from each study was used to calculate the final URF. The URFs were properly adjusted for covariates, e.g., smoking. The optimal exposure lag is recommended. Inclusion of workers with a minimum length of employment is important.

3.4.7.3 Reviewer 3

Rationales for the choice of the URFs from each study appear to be based on a thoughtful and well-articulated consideration of a range of relevant factors. In addition, analyses for a number of alternative options are also presented as a basis for comparison.

3.4.7.4 Reviewer 4

I am not convinced that the 7.4 year lag estimate is the best choice for calculating the final URF. Although it is the MLE of the lag for workers with a minimum of 1 year of employment, the model fit with a 7.4 year lag is not convincingly different than that with a 5 year lag based on the deviance shown in Table 6. When using a meta-analysis, you want to reduce inter-study variability as much as possible.

Maintaining the same lag time (5 years) and minimum length of employment (1 year) between both cohorts may be best. I recommend that TCEQ consider doing this.

3.5 Was the decision not to apply age-dependent adjustment factors (ADAFs) to the URF, to account for potential increased sensitivity of children, justified and properly considered given TCEQ guidance on evaluating the carcinogenic MOA (see Section 5.7.5 of TCEQ 2012)? (Charge Question 8)

3.5.1 Reviewer 1

Yes.

3.5.2 Reviewer 2

Since CrVI has not been demonstrated to have a mutagenic MOA for lung carcinogenicity, it is reasonable not to apply an age-dependent adjustment factor (ADAF) to the URF to account for potential increased sensitivity of children.

3.5.3 Reviewer 3

See comments above regarding the need for a stronger rationale for the conclusion that "CrVI has not been demonstrated to have a mutagenic MOA for lung carcinogenicity considering the reasonably scientifically-rigorous standard set under TCEQ guidelines"

(Question 5). In my view this necessarily requires additional analysis of the cited relevant references.

3.5.4 Reviewer 4

The decision not to apply the age dependent adjustment factor appears to be justified, primarily because the most likely MOA for lung tumors is the formation of reactive oxygen species that is expected to have a threshold for adverse effect due to the lung's innate capacity to reduce CrVI extracellularly. This capacity for reduction is physiologically-based and not likely to vary significantly among individuals of different ages. Thus, the use of a linear default, or even bi-modal MOA with a linear component, is highly conservative. Multiplying this conservative URF by an ADAF does not make physiological sense.

3.6 The final URF was derived using a meta-analysis approach that combined the two preferred URFs using a weighting based on inverse variance. Was this appropriate and does it result in a better URF and $^{chronic}ESL_{nonthreshold(c)}$? (Charge Question 9)

3.6.1 Reviewer 1

Yes it was appropriate to combine the two prefer URFs as done.

3.6.2 Reviewer 2

A meta-analysis approach that combines the two preferred URFs is appropriate. Inverse variance provides a measure of the precision of an estimate. That is, the smaller the variance of an estimate the better the precision and a higher weight (based on the reciprocal of the variance) is assigned to that estimate. This provides a better estimate of the URF and effect screening level (ESL).

3.6.3 Reviewer 3

Given the variations between the design of the two studies and populations examined, I wondered if any thought had been given to consideration at least semi-quantitatively of the relative uncertainty of study specific URFs as a basis for selection of an optimum value, rather than the combined approach weighted only on the basis of inverse variance (See comments below on uncertainty analysis).

3.6.4 Reviewer 4

I agree with TCEQ that neither the Baltimore nor the Painesville cohort is better than the other in terms of study design and interpretation of results. Thus, I agree with the use of TCEQ's meta-analysis approach. Since some of the glaring issues of the Baltimore cohort were corrected by limiting the minimum duration of employment and by using the Cox modeling approach, I feel comfortable that combining the two URFs is appropriate. The weighting approach used was also appropriate.

However, note that the Baltimore cohort (Gibb et al. 2000), which has more uncertainty due to study design issues, is weighed more heavily than the Painesville cohort (Crump et al. 2003) (55.6% of the weight versus 44.4%, respectively) for the derivation of the final URF. This appears to be counter-intuitive, TCEQ might recheck this weighting.

4. Peer Reviewer Responses to Additional Questions

4.1 Appendix E presents an uncertainty analysis. Have all the key uncertainties been identified? Are the conclusions regarding these uncertainty issues and their impact on the URFs correct and discussed? (Charge Question 10)

4.1.1 Reviewer 1

I think Appendix F presents a reasonable uncertainty analysis.

4.1.2 Reviewer 2

The key uncertainties have been identified. The conclusions regarding the uncertainty issues and their impact on the URFs are adequately discussed and appear to be correct.

4.1.3 Reviewer 3

The authors appropriately note that many of the presented uncertainties are common to risk assessments based on epidemiological studies. I wondered if there had been any thought given to providing more specific figurative representation of the calculated URFs with visual "bounding" based on consideration of their relative uncertainty. The objective is to additionally clarify confidence in the various outputs, based on at least semi-quantitative assessment of the impact of stated uncertainties, in a relative context.

4.1.4 Reviewer 4

I think some of the key uncertainties have been identified in Appendix E. Section E.2 is particularly important since the URF is intended for the general population, not just healthy workers. Uncertainties due to sex, age (i.e., children, adolescents, and/or elderly), and race need to be carefully considered and TCEQ appears to have done this in its evaluation of the ADAF.

However, I would like to see some information on susceptibility and sensitivity beyond TCEQs assertion that background lung cancer rates are similar (or lessened) among these groups than among workers.

4.2 Please identify any other relevant issues or questions that are important for the review of this assessment. (Charge Question 11)

4.2.1 Reviewer 1

I have no substantive issues with the risk assessment. One formatting issue: the Table numbers in the text do not seem to correspond to the relevant Tables.

4.2.2 Reviewer 2

The Table numbers in the text do not match the actual Table numbers.

4.2.3 Reviewer 3

Justification for the dosimetric adjustment (Section 4.2.3.1.5) should be included since many effects on the lung are concentration – related.

4.2.4 Reviewer 4

I was surprised at the frequent use of inappropriate precision throughout the text. As TCEQ knows well, the wrought risk assessment values are generally no more precise than one digit. Listing these values with two digits of precision is problematic since managers will then consider these values appropriate at two digits. Using three digits of precision is scientifically incorrect.

Several marginal comments are listed in the table below for consideration.

Section Number	Page Number	Comment
3.1.2	2	This is a well written section, with enough text to be convincing, even if one only has a passing understanding of chromium's toxicity.
3.1.2	2	*"These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids."* - use the word "chemicals" instead of "species"
3.1.2	3	*"Cellular damage from exposure to many chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity."* - Well, we presume that this hypothesis has been previously stated; this is the first time it is mentioned in this section.
4.2.1	4	*"Particulate forms of CrVI, relatively water insoluble compounds more specifically (e.g., moderate to low solubility), appear to be more potent lung carcinogens, with extracellular dissolution of the CrVI compound critical to activity."* - It is not readily apparent from this text in which direction the dissolution of CrVI takes the toxicity: more toxic or less?

4.2.1	5	*"Consistent with these WOE classifications, the TCEQ considers CrVI and CrVI compounds as a group to be carcinogenic to humans via inhalation (at least at sufficiently high long-term doses)."* - I agree with the WOE classification and its application to all CrVI forms.
4.2.3	7	*"More specifically, for comparison of nonlinear-threshold assessment results to the TCEQ policy-based 1 in 100,000 excess target risk air concentration calculated using the default linear low-dose URF approach."* - This is not a complete sentence. Suggested revision: More specifically, these authors compared the nonlinear...
4.2.3	8	*"...derives a potential cancer-based chronic ReV of 0.24 µg CrVI/m3 following dosimetric adjustments and application of appropriate UFs (total UF of 30).*" - non-linear ReV of 0.24 µg/m^3
4.2.3.1.2	8	*"Thus, the dose metric used for the dose-response assessment is cumulative CrVI exposure..."* - I am ok with the choice of this dose metric.
4.2.3.1.3.1	9	All the stated risks in this paragraph are too precise.
4.2.3.1.3.1	9	*"...estimated the slope of the linear relative risk model with multiplicative background as 0.636"* - What are the units of the slope? Risk per person-year?
4.2.3.1.3.1	10	*"...estimates based on Crump et al. (2003) are given in Table 8 below."* - Table numbers throughout this text do not appear to be correct.
4.2.3.1.3.2	11	*" ...≥ 5 years for the Baltimore cohort"* - *of* the Baltimore cohort

4.2.3.1.3.2	11	*"As can be seen..."* - Moreover, as can be...
4.2.3.1.3.2	11	*"and to increase SMRs for..."* - use "have increased" instead of "to increase"
4.2.3.1.3.2	11	*"...(important when short-term, low- dose workers are used as the referent) and the general population (important when the general population is the referent as in Gibb et al. 2000)."* - These two parentheticals seem to be important, but I do not understand the context in which they are being used. Please expand the text a bit here.
4.2.3.1.3.2	11	*"the exposure scenario they experienced..."* - use "the Baltimore cohort" instead of "they"
4.2.3.1.3.3	14	*"...are given in Table 9 below."* - This is Table 2, correct?
4.2.3.1.3.3 Table 2.	14	Why is the expected value different in each group? Are these values not standardized?

5. References

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Appendix A
Peer Reviewer Biographical Sketches

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Appendix A - Peer Reviewer Biographical Sketches

Experts Selected by TERA to Peer Review TCEQ Hexavalent Chromium Section 4.2 Carcinogenic Potential - Developmental Support Document, May 2013

TERA independently selected the following four experts to provide independent peer review of the TCEQ document. Each has been screened for conflict of interest. None of the selected experts has a conflict of interest with the review of this document.

Michael L. Dourson, Ph.D., D.A.B.T.

Dr. Michael Dourson is the President of Toxicology Excellence for Risk Assessment (TERA). He has a PhD in toxicology from the University of Cincinnati and is a Diplomate of the American Board of Toxicology (ABT). He has lead TERA's development of partnerships among diverse groups to address chemicals of high visibility, such as formaldehyde, perchlorate, chloroform, and soluble nickel, and cooperative ventures such as the Voluntary Children's Chemical Exposure Program, the International Toxicity Estimates for Risk database (available at Toxnet), and the Alliance for Risk Assessment. He worked 15 years for EPA, holding several leadership roles and winning awards for joint efforts, such as the creation of EPA's Integrated Risk Information System. In 2003, he won the Society of Toxicology (SOT) Lehman award for major contributions that improve the scientific basis of risk assessment and in 2009 he won the International Society of Regulatory Toxicology and Pharmacology's International Achievement Award. He was also selected a Fellow for the Society for Risk Analysis (SRA) for substantial achievement in science relating to risk analysis and service to SRA and as a Fellow of the Academy of Toxicological Sciences. Dr. Dourson has co-published more than 100 papers on risk assessment methods, including methods for assessing risk in sensitive subgroups, on use of animal and human data in the assessment of risk, or on assessments for specific chemicals. He has also co-authored well over 100 government risk assessment documents, made over 100 invited presentations, and chaired well over 100 sessions at scientific meetings and independent peer reviews. He has been elected to multiple officer positions in the American Board of Toxicology, the Society of Toxicology (SOT), and the Society for Risk Analysis. He serves on EPA's Science Advisory Board, is vice chair of the NSF International Health Advisory Board, and serves on the editorial board of several journals.

David Gaylor, Ph.D.

Dr. David Gaylor received a B.S. and M.S. degree in Statistics from Iowa State University and a Ph. D. in Statistics from North Carolina State University. Dr. Gaylor, whose expertise is in the fields of biometry, statistics, and health risk assessment, currently is an independent consultant. Previously, Dr. Gaylor retired from the National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), where he was the Director of the Biometry and Risk

Assessment Division. In that position, Dr. Gaylor developed experimental protocols and provided statistical analyses of experiments in carcinogenesis, teratogenesis, mutagenesis, and neurotoxicity, and developed techniques to advance the science of quantitative health risk assessment. Dr. Gaylor also serves as an Adjunct Professor of Statistics at the University of Arkansas for Medical Sciences. Dr. Gaylor is a Fellow of the American Statistical Association, the Society for Risk Analysis, and the Academy of Toxicological Sciences. Dr. Gaylor has served on more than 70 national and international work groups and committees on many aspects of biometry, toxicology, and risk assessment. He is currently a member of the editorial board of three professional journals: Human and Ecological Risk Assessment; Toxicology and Industrial Health; and Regulatory Toxicology and Pharmacology. Dr. Gaylor has authored or coauthored more than 160 journal articles, 25 book chapters, and made over 100 presentations at scientific meetings on bio-statistics and a wide range of health risk assessment issues. Many of Dr. Gaylor's publications address dose response assessment, bio-statistics, and quantitative risk assessment.

M.E. (Bette) Meek, Ph.D., M.Sc

Dr. Bette Meek is currently the Associate Director of Chemical Risk Assessment at the McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, where she has recently completed an interchange assignment from Health Canada. She has extensive experience in the conduct and management of chemical risk assessments within the Government of Canada, having managed most recently, the program of health assessments of Existing Substances under the Canadian Environmental Protection Act (CEPA) and previously, those related to contaminants in drinking water and air. Experience on Existing Substances included the precedent setting mandate to consider priorities for assessment from amongst the 23, 000 substances on the Domestic Substances List. With colleagues within Canada and internationally, she has contributed to or led initiatives to increase transparency and efficiency in chemical risk assessment, having convened and participated in initiatives in this area for numerous organizations including the International Programme on Chemical Safety and the Organization for Economic Cooperation and Development. Areas of contribution have included the development of frameworks for weight of evidence analysis including mode of action, chemical specific adjustment factors, physiologically-based pharmacokinetic modeling, combined exposures and predictive modeling. She has also authored over 175 publications in the area of chemical risk assessment and received several awards for contribution in this domain. Dr. Meek has a background in toxicology receiving her M.Sc. in Toxicology (with distinction) from the University of Surrey, U.K. and her Ph.D. in risk assessment from the University of Utrecht, the Netherlands

Kyle Steenland, Ph.D.

Dr. Kyle Steenland is an environmental/occupational epidemiologist who is a professor in the Environmental Health Department at the Rollins School of Health, Emory University. He has

been at Emory for 10 years and teaches advanced epidemiologic methods to students at the Rollins School of Public Health. Prior to working at Emory, he worked for 20 years at the National Institute for Occupational Safety and Health (NIOSH). Dr. Steenland has published over 100 first-authored articles in the field, and edited two textbooks. He has conducted a large number of cohort studies, including both mortality and cancer incidence studies (e.g., cohorts of workers exposed to dioxin, ethylene oxide, welding fumes, sulfuric acid mists, silica, diesel fumes, and polychlorinated biphenyls). He is currently conducting two large cohort studies of community residents and workers exposed to perfluorooctanoic acid (PFOA), and to lead. He has also published a number of studies on epidemiologic methods, including exposure-response analyses, adjustment for multiple comparisons, the effect of measurement error, and the attributable fraction.

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Appendix B
Charge Questions and Instructions to Reviewers

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Appendix B - Charge Questions and Instructions for Peer Reviewers

Introduction and Instructions

The peer reviewers are asked to provide their opinions and comments on specific and general questions. For each response (including the Yes/No questions), please explain your reasoning and considerations, discuss scientific support for your comments and opinions, and identify the sources you consulted to construct your response. Please address each charge question by adding your answers to this Word document; and reference the TCEQ document page, paragraph, and line number, where appropriate.

Background

The Toxicology Division of the Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that outlines the hazard assessment and dose-response processes used to derive health-protective Effects Screening Levels (ESLs) and Reference Values (ReV) for hexavalent chromium (CrVI). The draft DSD includes Section 4.2, which documents the derivation of an inhalation unit risk factor (URF) and air concentrations corresponding to the policy-based 1 in 100,000 excess risk level based on lung cancer mortality. These toxicity values are used in the evaluation of air permit applications and ambient air data and were developed using RG-442 TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). The TCEQ guidelines can be found at http://www.tceq.texas.gov/publications/rg/rg-442.html.

We are asking you to provide a review of the scientific approaches used by TCEQ in developing the URF for CrVI as described in the Carcinogenic Potential (Section 4.2) of the draft DSD. The DSD is a summary document and does not provide a detailed description of every aspect of the toxicity assessment for a chemical. References to appropriate papers or documents are provided if more detailed information is needed. Please contact Melissa Vincent (Vincent@tera.org) if you wish to see a copy of any of the cited references.

There are a number of policy decisions the TCEQ has made and included in this assessment that they do not seek comment on. For example, risk management goals were approved by the Commissioners and Executive Director of the TCEQ and are consistent with other TCEQ programs. Therefore, please do not spend your time commenting on the policy-based excess risk level (1E-05) and default lifetime exposure assumption of 70 years.

General Questions

Please evaluate strengths and weaknesses of the procedures used to develop the URF based on the specific questions described below. Where possible, try to put the strengths and weaknesses in perspective by indicating their relative magnitude. Please try to avoid emphasizing minor technical details or making tutorial comments. Reviewers should identify scientific uncertainties and suggest ways to reduce or eliminate those uncertainties.

1. Does the draft DSD clearly describe the approaches used by TCEQ to develop the URF?

2. Were procedures outlined in RG-442 *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012) followed by the TCEQ in this assessment?

3. Please identify any relevant studies or data that have not been cited and would affect an important part of the assessment and explain how they would impact the assessment specifically.

Cancer Assessment and Unit Risk Factor (URF)

The draft CrVI DSD describes the approaches used to evaluate carcinogenicity and derive the URF and the chronic ESL (at the 1E-05 excess risk level) for cancer in Section 4.2. Please review the key decisions made by TCEQ in deriving these values.

In formulating your response to each question, please consider and comment on the consistency of the assessment with TCEQ's RG-442 guidelines, the scientific appropriateness of the decision or conclusion, and any additional approaches or additional information that would improve that decision/conclusion.

4. Section 4.2.1 presents carcinogenic weight of evidence classification information and conclusions of authoritative bodies. Is TCEQ's weight of evidence conclusion appropriate? If not, what alternative conclusion is appropriate and why? Is the decision to apply the URF to all forms of CrVI appropriate for public health protection purposes?

5. Section 4.2.2 discusses hexavalent chromium's carcinogenic mode of action (MOA). Have the authors clearly and accurately summarized the proposed hypotheses for the MOA, given the current state of knowledge? (NOTE: Please keep in mind that the purpose of the DSD is to document the derivation of the URF and ESL as opposed to being a comprehensive weight of evidence paper on the MOA. Therefore, if data on the MOA are not sufficient to justify an alternate approach to linear low-dose extrapolation, the DSD only needs to generally summarize the primary proposed MOAs, MOA issues, and justify use of the default extrapolation method [see next question].

6. In Section 4.2.3 TCEQ provides a rationale for not using a nonlinear-threshold dose response approach; do you agree with TCEQ's conclusion that there is not adequate scientific justification to deviate from use of the default linear low-dose extrapolation approach given the inherent uncertainties of available data?

7. *Please comment on the following key decisions in the TCEQ assessment. For each, please discuss if the conclusions and choices are supported by the available data and discuss any additional information, data, or analyses that could improve the decision.*

a. Do you agree that lung cancer mortality is the best cancer endpoint for this dose-response assessment? Are lung cancer incidence and mortality sufficiently similar as to be comparable for purposes of this assessment for the reasons discussed in the DSD?

b. Cumulative CrVI exposure (mg CrVI/m^3-yr) was chosen as the dose metric.

c. Were the most appropriate human epidemiological studies (Painesville Ohio and Baltimore Maryland cohorts; Crump et al. [2003] and Gibb et al. [2000]) selected for the dose-response assessment and was their selection sufficiently described and justified? Are there any other published epidemiological studies of inhaled hexavalent chromium exposures with sufficient data that should and could have been considered by TCEQ in deriving the URF?

d. Were the data from supporting cohorts (Leverrkusen and Uerdingen, Germany; Corpus Christi, Texas; and Castle Hayne, North Carolina) and Applied Epidemiology (2002) used appropriately? Additionally, were the reasons for excluding the URF based on the data from these supporting cohorts (Leverrkusen and Uerdingen, Germany; Corpus Christi, Texas; and Castle Hayne, North Carolina) and Applied Epidemiology (2002) appropriate and sufficiently described?

e. Were the statistical and modeling approaches used to calculate the slope (β) estimates (Section 4.2.3.1.4) and URFs (Section 4.2.3.1.6) for the selected data sets appropriate?

f. Is use of the central estimate of the URFs sufficiently discussed and justified?

g. Are the most appropriate URFs from each study used to calculate the final URF? That is, was the choice of URFs for decision making the best choice – properly adjusted for covariates, based on the optimal exposure lag, and based on the inclusion of workers with a minimum length of employment?

8. Was the decision not to apply age-dependent adjustment factors (ADAFs) to the URF, to account for potential increased sensitivity of children, justified and properly considered given TCEQ guidance on evaluating the carcinogenic MOA (see Section 5.7.5 of TCEQ 2012)?

9. The final URF was derived using a meta-analysis approach that combined the two preferred URFs using a weighting based on inverse variance. Was this appropriate and does it result in a better URF and $^{chronic}ESL_{nonthreshold(c)}$?

Other Questions

10. Appendix E presents an uncertainty analysis. Have all the key uncertainties been identified? Are the conclusions regarding these uncertainty issues and their impact on the URFs correct and discussed?

11. Please identify any other relevant issues or questions that are important for the review of this assessment

Appendix C
Public Comments

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Appendix C - Public Comments

Public Comment 1

The following comments were submitted by:

Loren Raun, PhD.
Bureau for Pollution Control and Prevention
For the City of Houston, Texas

Thank you for giving the City of Houston (City or Houston) the opportunity to comment on important changes to the hexavalent chromium toxicity value and associated screening levels presented in the Final Draft of the Development Support Document dated March 2013. The findings in this document indicate that the Effect Screening Level (ESL) for this chemical will be lowered from 0.01 to 0.0043 mg/m^3. The deadline for filing comments in March 24, 2013. The City of Houston endorses this change with the following comments.

Hexavalent chromium (CrVI) is an important air toxic of concern in the City of Houston. As early as 2006 it was identified as one of twelve air pollutants posing a definite risk to Houstonians and as recently as 2012 it has been found in the ambient air downwind of some metal recycler facilities at unhealthy levels. Prior to the discovery of CrVI downwind of metal recyclers, it had remained un-monitored and all discussions of risk to the community from this contaminant were based on modeling. We believe that the decrease in the ESLs should be accompanied by an increase in actual monitoring of this chemical.

In addition, we have noted that no adjustments have been made for childhood exposure because there currently is not information on the differential effect on children. The TCEQ states that it will review it in the future. Because the locations where the City of Houston has found elevated risk from ambient concentrations are residential, we are anxious that TCEQ re-examine the risk to children in a timely manner so that children are adequately protected.

Finally, we remain of the opinion that a screening level is more appropriate at the 1:1,000,000 risk limit and the 1:100,000 is more correctly an action level.

References:

Sexton, K., Linder, S., Abramson, S., Bondy, M. Delclos, G, Fraser, M., Stock, T., Ward, J., (2006). "*A Closer Look at Air Pollution in Houston: Identifying Priority Health Risks, Report of the Mayor's Task Force on the Health Effects of Air Pollution*"; Institute for Health Policy Report ES-001-006, Prepared for the City of Houston by The Institute for Health Policy, University of Texas School of Public Health, , Health Science Center at Houston. Available at: http://www.sph.uth.tmc.edu/uploadedFiles/Centers/IHP/Report_Body.pdf

Raun, L., Pepple, K., Hoyt, D., Blanco, A., Richner, D., and Li, J. (2012). Community scale air pollution area sources and public health: Assessing risk from an under-regulated area source of metal particulate, Environmental Impact Assessment Review, October 2012.

Public Comment 2

The following comments were submitted by:

Tania Onica, M.Sc.
Senior Regulatory Toxicologist
Human Toxicology and Air Standards Section
Standards Development Branch
Ministry of the Environment

Charge Question 3. Please identify any relevant studies or data that have not been cited and would affect an important part of the assessment and explain how they would impact the assessment specifically.

I felt that much of the MOA section lacks sufficient supporting evidence and raises questions. For example:

Excerpt	Comment
*"However, TCEQ (2012) indicates there should be a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA and the TCEQ believes such a standard has **not** been met for CrVI (i.e., merely demonstrating plausibility is not tantamount to an adequately robust demonstration that mutagenicity is in fact THE initiating event in target tissues)."*	Although certain theories of carcinogenicity are briefly mentioned (Holmes et al., 2008; Tox Strategies, 2012; Zhitkovich et al., 2011, etc.), the theories don't appear to be reviewed in any detail. In order to lend support to the above statement (or any other MOA hypothesis), I suggest that a more detailed MOA analysis is carried out, which would be critical in in developing a more data-informed value. (I understand that the purpose of the DSD is not a comprehensive WOE paper on the MOA. However, I find the current write-up confusing. If the standard for scientific rigour has not been met for Cr(VI), why is a linear extrapolation being carried out?)
"CrVI carcinogenicity/toxicity appears to be mediated through reactive intermediates (e.g., CrIII, oxygen radicals) generated during the rapid intracellular reduction of CrVI to CrIII, which is the final product of intracellular CrVI reduction"	Although cited by TCEQ in a different sections, O'Brien 2003 and Zhitkovich 2005 suggests that radical formation is likely limited under physiological conditions, where the formation of sequential electron transfers is restricted due to millimolar ascorbate concentrations. This suggests a diminished role for radical species in Cr(VI) carcinogenicity and should be discussed in more details.
"These MOA concepts are consistent with ATSDR (2012) indicating that CrVI absorption	As reviewed by Harvey Clewell for OSHA (2006) cell uptake will occur concurrently

into tissues may be a function of doses high enough to overwhelm CrVI reduction mechanisms and the results of a recent oral carcinogenic MOA analysis (Thompson et al. 2011)."	and in parallel with extracellular reduction). Thus, even at low Cr(VI) concentrations where the reductive capacity is undiminished, a fraction of Cr(VI) will still be taken up into cells, be reduced to Cr(III) and may interact with DNA. This is inconsistent with what is presented in the TCEQ document.

Cancer Assessment and Unit Risk Factor (URF)

Charge Question 4. Section 4.2.1 presents carcinogenic weight of evidence classification information and conclusions of authoritative bodies. Is TCEQ's weight of evidence conclusion appropriate? If not, what alternative conclusion is appropriate and why? Is the decision to apply the URF to all forms of CrVI appropriate for public health protection purposes?

As discussed in the answer to question #3, I felt that the WOE analysis of the MOA could be examined more thoroughly and presented to the reader in more details.
Regarding whether the URF applies to all forms of Cr(VI), irrespective of solubility, for public health protection, is appropriate as insoluble compounds have slower clearance and longer residence time in the lung, which may enhance their carcinogenic potential.

Section 4.2.2 discusses hexavalent chromium's carcinogenic mode of action (MOA). Have the authors clearly and accurately summarized the proposed hypotheses for the MOA, given the current state of knowledge? (NOTE: Please keep in mind that the purpose of the DSD is to document the derivation of the URF and ESL as opposed to being a comprehensive weight of evidence paper on the MOA. Therefore, if data on the MOA are not sufficient to justify an alternate approach to linear low-dose extrapolation, the DSD only needs to generally summarize the primary proposed MOAs, MOA issues, and justify use of the default extrapolation method [see next question].

As discussed in the answer to question #3, I felt that many aspects of the MOA discussion should be examined more thoroughly and presented to the reader in more details. And given that "***if data on the MOA are not sufficient to justify an alternate approach to linear low-dose extrapolation, the DSD only needs to generally summarize the primary proposed MOAs, MOA issues, and justify use of the default extrapolation methods"*** why does TCEQ state: "*However, TCEQ (2012) indicates there should be a reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA and the TCEQ believes such a standard has* ***not*** *been met for CrVI…"?* The document as written, appears biased in favour of a threshold-like analysis, yet derives a value based on linear extrapolation. This is confusing to the reader.

Charge Question 6. In Section 4.2.3 TCEQ provides a rationale for not using a nonlinear-threshold dose response approach; do you agree with TCEQ's conclusion that there is not adequate scientific justification to deviate from use of the default linear low-dose extrapolation approach given the inherent uncertainties of available data?

I do believe that at this time, linear extrapolation is the most appropriate option given that more sophisticated modelling techniques have not yet been developed to account for the non-linear kinetics (dissolution, extracellular reduction, cellular uptake as well as the homeostatic response to depletion of reductive resources) of Cr(VI). I also believe that selecting a crude point of departure and applying uncertainty factors (as carried out in Haney et al., 2012) is also an overly-simplistic approach to address this. These points have been previously mentioned by Harvey Clewell for OSHA (2006) and Lynne Haber for TERA (2008).

References

Haber, L. (2008). TERA. (Personal Communication). Comments on: Ontario Ministry of the Environment Science Discussion Document on Hexavalent Chromium.

O'Brien, T.J., Ceryak, S., Patierno, S.R. (2003). Complexities of chromium carcinogenesis: Role of cellular response, repair and recovery mechanisms. Mutat Res. 533(1-2):3-36.

OSHA (Occupational Safety and Health Administration) (2006). Occupational exposure to hexavalent chromium; final rule. Code of Federal Regulations. Occupational Safety and Health Administration. 29 CFR 1910, 1915, et al. Available at http://www.osha.gov/FedReg_osha_pdf/FED20060228.pdf.

Zhitkovich, A. (2005). Importance of chromium-DNA adducts in mutagenicity and toxicity of chromium(VI). Chem Res Toxicol. 18(1):3-11.