Texas Commission on Environmental Quality
Responses to Comments Received on the

Hexavalent Chromium Development Support Document
Section 4.2 – Carcinogenic Potential
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INTRODUCTION

Toxicology Excellence for Risk Assessment (TERA) supported the Texas Commission on Environmental Quality (TCEQ) by conducting an external expert peer review as a letter peer review of Section 4.2 (Carcinogenic Potential, Draft March 2013) of the Development Support Document for Hexavalent Chromium. The review materials, including the draft document, charge to reviewers, and key references (available at http://www.tera.org/Peer/crvi/index.html) were distributed to the panel in May 2013. External expert panel members reviewed draft Section 4.2 of the Development Support Document (DSD) and submitted written comments that addressed the charge questions in May 2013. These written comments represent the panel's review of the carcinogenic potential section (Section 4.2) of the draft hexavalent chromium DSD. A June 17, 2013 report containing expert panel member comments was prepared by TERA and is available at the above-referenced website. The written comments submitted by the expert panel and the TERA report comprise the complete peer review of Section 4.2 (Carcinogenic Potential) of the draft hexavalent chromium DSD.

The Toxicology Division (TD) of the TCEQ appreciates the significant effort put forth by the panel members to provide technical comments on carcinogenic potential section (Section 4.2) of the draft DSD for hexavalent chromium. The TD made appropriate revisions to the March 2013 draft DSD based on panel member comments consistent with the goal of the TCEQ to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD) given the studies available and use of the derived values (i.e., evaluation of ambient air data and air permit applications). The TD's careful consideration and evaluation of expert panel member comments furthered that goal. The comments within each section below correspond to a specific charge question. The comments are followed by TCEQ responses which include what changes, if any, were deemed appropriate and made to the draft DSD in response to the comment. Similarly, public comments made by the City of Houston and the Ontario Ministry of the Environment (contained in TERA's expert panel review report) are addressed in Section 4.

Please refer to Haney et al. (2014) for the published manuscript "Development of an inhalation unit risk factor for hexavalent chromium."

Panel Written Comments

The purpose of this document is to provide responses to comments from the panel, with any potentially significant issues being of particular interest. When necessary, lengthy comments were divided into smaller sections and separate responses provided. Written comments on the same issue which appear in more than one section of the written comments (i.e., reiterated written comments) may only be stated and addressed once below to avoid redundancy. Extraneous text contained in written comments is also not provided below, such as text extraneous to the charge question posed, text unnecessary for an understanding of the potential issue identified, etc. *While responding to some expert panel member comments required revisions to the text (e.g., clarifications, additional language or discussion), as can be seen below, no comments identified issues which affect the draft inhalation unit risk factor (URF) for hexavalent chromium and compounds.*

1. General Questions

1.1 Approaches used by TCEQ to develop the URF

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

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 section (p 27) where the final numbers are present

Response: Additional descriptive text was added to the DSD per the comment.

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.

Response: TCEQ appreciates this positive feedback.

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?).

> **Response:** TCEQ appreciates the positive feedback in the first paragraph. Descriptive text was added to the DSD per the comments in the second paragraph.

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).

> **Response:** TCEQ appreciates the positive feedback in the first paragraph. A response to the Reviewer #4 recommendation for an alternative approach, which in some ways is less conservative than the linear low-dose extrapolation procedure employed in Section 4.2 of the draft DSD, is provided below under question 6. See the responses below regarding the potential textual clarifications referred to by this reviewer.

1.2 Procedures Followed by the TCEQ

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

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

Reviewer #4: I believe so.

> **Response:** TCEQ appreciates the positive feedback.

1.3 Relevant Studies or Data

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.

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 of the occupational standard from 52 to 5 µg/m^3.

> **Response:** A comparison of an occupational assessment based on a worker exposure scenario and an inhalation URF assessment for the general public derived assuming a lifetime of environmental exposure is beyond the scope and purpose of the DSD. The differences would be numerous (see below). Regarding the ultimate regulatory air concentrations, based on the final URF in the draft DSD (2.3E-03 per µg CrVI/m^3) the air concentration corresponding to an excess lung cancer risk of 1 in 100,000 is 0.0043 µg CrVI/m^3, which is approximately 1,163 times lower than the 5 µg CrVI/m^3 occupational value cited by Reviewer #1.
>
> For purposes of this response, note that 5 µg CrVI/m^3 is an occupational concentration corresponding to an excess risk of 1 in 1,000 for an exposure period of 45 years (20 to 65 years of age), 5 days per week, and 8 out of 24 hours per day, based on Gibb et al. (2000). This is opposed to TCEQ's 0.0043 µg CrVI/m^3 which is an environmental concentration corresponding to an excess risk of 1 in 100,000 for 70 years, 7 days per week, and 24 hours per day, based on Gibb et al. (2000) and Crump et al. (2003). If OSHA's PEL of 5 µg CrVI/m^3 is converted to an environmental continuous exposure corresponding to an extra risk of 1 in a 100,000, then the equivalent concentration is 5 x (45/70) x (5/7) x (8/24) x (0.00001/0.001) = 0.0077 µg CrVI/m^3, which is only 1.78-fold greater than the value of 0.0043 µg CrVI/m^3 derived by TCEQ (this calculation assumes that OSHA is also using 70 years as the age for risk calculations and that there are no other adjustments that OSHA may have done).

Reviewer #2: Not aware of additional relevant studies or other important data.

> **Response:** No comment needed.

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".

> **Response:** These additional references are noted. The referenced text in the DSD was revised pursuant to this comment and related comments below from this reviewer.

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, we 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.

> **Response:** No comment needed.

2. Cancer Assessment and Unit Risk Factor (URF)

2.1 Carcinogenic Weight of Evidence Classification

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?

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

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, consistent with public health protection policy.

Response: TCEQ appreciates this positive feedback.

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. TCEQ may wish to discuss this for chromium compounds as well, or at least reference the nickel discussion [Goodman et al. 2011].

Response: TCEQ appreciates the positive feedback in the first paragraph. While comments in the second paragraph are not relevant to the charge questions posed under this section, additional clarifying text was added to the DSD pursuant to the comments.

2.2 Carcinogenic Mode of Action

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?

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** A comparative weight of evidence for various potential MOAs is beyond the scope of the DSD and would not change the conservative extrapolation approach (i.e., linear low-dose extrapolation) ultimately adopted by the DSD. An extensive and comprehensive MOA weight of evidence analysis is not necessary for purposes of the DSD and is better left to papers in the scientific peer reviewed literature which focus

> exclusively on this issue (as cited in the DSD). 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. This reviewer acknowledges, "I believe that TCEQ has presented a clear summary of the hypothesized modes of action, based on available data." Furthermore, although Haney et al. (2012) is referenced: (1) it is not the focus of the document; (2) adoption of the linear low-dose extrapolation approach in the DSD does not rely on the MOA information presented in Haney et al.; and (3) it was peer reviewed prior to publication and explicitly states, "It should be noted that the intent of the current study is not to perform an exhaustive weight of evidence evaluation of all data potentially relevant to the MOA (or MOAs), but rather to present available summary MOA information and statistical evidence interpreted as consistent with (albeit not proof of) a potential practical threshold for CrVI-induced inhalation carcinogenicity..." Nevertheless, the referenced sentence in the DSD was revised pursuant to the comment.

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.

> **Response:** Regardless of whether CrVI escaping reduction to enter target tissue cells comfortably fits into the key events of an MOA as normally or historically envisioned in guidance, this is a *de facto* key event in the broader sense at very least in the chemical-specific case of CrVI toxicity. That is, this must occur (i.e., is key) upstream of any scaling between species because in its absence there are no CrVI-induced toxicological effects requiring interspecies scaling of dose or consideration of intrahuman variability.

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 inform estimates of risk.

> **Response:** The DSD does not propose this argument, only cites Haney et al. which makes an argument for simply "consideration" of nonlinear-threshold approaches in the context of additional MOA-relevant information. Furthermore, the DSD does not actually rely on Haney et al. (2012) for adoption of the linear low-dose extrapolation approach employed therein (i.e., all reference to it could be removed and the carcinogenic dose-response assessment would be entirely unaffected). Nevertheless, as indicated above, the referenced sentence in the DSD was revised pursuant to the comment.

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.

> **Response:** Additional text has been added to the DSD regarding considerations relevant to TCEQ's conclusion that a mutagenic MOA has not been adequately demonstrated.

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.

> **Response:** TCEQ appreciates the positive feedback in the first paragraph. In regard to the comments on linear low-dose extrapolation in the second paragraph (below the bullets), when the MOA is unknown ("the scientific community has not reached a consensus on the specific MOA(s) for CrVI-induced lung carcinogenesis") or information on the carcinogenic MOA suggestive of low-dose nonlinearity is not adequately robust to sufficiently support an alternate approach for the protection of public health with an acceptable level of scientific certainty (as is the case with CrVI), linear low-dose extrapolation is used as a conservative default by regulatory agencies. A response to the Reviewer #4 recommendation for an alternative approach, which in some ways is less conservative than the linear low-dose extrapolation procedure employed in Section 4.2 of the draft DSD, is provided below under question 6.

2.2 Rationale for Not Using a Nonlinear-Threshold Dose Response Approach

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.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates the positive feedback and the text referencing Haney et al. was revised pursuant to the comment.

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.

> **Response:** TCEQ acknowledges the main point implied by the comment that the default linear approach is perhaps no more justified than a nonlinear-threshold dose response approach. However, TCEQ believes information on the carcinogenic MOA suggestive of low-dose nonlinearity is not adequately robust to sufficiently support a specific alternate approach for the protection of public health with an acceptable level of scientific certainty (as is the case with CrVI). In such cases regulatory agencies err on the side of conservatism (potentially overestimating risk) and linear low-dose extrapolation is used as a conservative default regardless of whether available MOA data clearly justify its use (i.e., the absence of MOA data deemed to adequately support an alternate plausible approach triggers use of the conservative default approach), at least until more definitive MOA information adequately supporting a particular alternate approach is available.

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.

> **Response:** The DSD has been revised to mention the possibility of a dual MOA and that existing modeling results could be reflective of this.

2.3 Is Lung Cancer Mortality The Best Cancer Endpoint?

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?

Reviewer #1: Yes incidence and mortality are essentially equivalent for lung cancer.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback. Lung cancer mortality is the endpoint available for this dose-response assessment, and Reviewer #3 agrees that lung cancer mortality is sufficiently similar to incidence and the best cancer endpoint. As Reviewer #4 indicates, currently available data preclude the use of incidence.

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).

> **Response:** TCEQ appreciates this positive feedback.

2.4 Cumulative CrVI Exposure as the Dose Metric

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

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.

> **Response:** TCEQ appreciates this positive feedback regarding the dose metric. The referenced clarifying language on Park et al. (CrVI versus CrO_3) from Appendix A was added to the main text of the DSD.

Reviewer #2: From the available data on exposure, cumulative CrVI exposure (mg CrVI/m^3-yr) appears to be the best dose metric.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates the positive feedback in the first paragraph. The primary reason that exposure concentration was not used is because the only dose metric available for the Painesville data is cumulative exposure. Furthermore, cumulative exposure is the dose metric most commonly used in epidemiological studies and it has the advantage that it combines both exposure intensity and exposure duration

Reviewer #4: This exposure metric is appropriate.

> **Response:** TCEQ appreciates this positive feedback.

2.5 The Most Appropriate Human Epidemiological Studies

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?

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

2.6 Data from Supporting Cohorts

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?

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

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.

Response: TCEQ appreciates this positive feedback.

2.7 Statistical and Modeling Approaches

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?

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).

Response: TCEQ appreciates the positive feedback and clarifying text regarding the Cox modeling was added to the DSD.

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) is correctly described in Section 4.2.3.1.6.

Response: TCEQ appreciates this positive feedback.

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 thoughtful and well articulated consideration of a range of relevant factors.

Response: TCEQ appreciates this positive feedback.

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…"

Response: TCEQ appreciates the positive feedback in the first paragraph. The reviewer is correct that Cox proportional hazards modeling cannot be performed for the Crump et al. (2003) cohort due to the lack of required information. Clarifying text was added to the DSD.

2.8 Central Estimate of the URFs

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

Reviewer #1: Yes.

Response: TCEQ appreciates this positive feedback.

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.

Response: This reviewer appears to have misinterpreted the charge question and/or approach utilized in the DSD. Regardless, TCEQ agrees with Reviewers #1 and #4 that clearly indicated use of the central estimates is justified. The text in the DSD was revised to indicate more clearly that the URF was calculated using the central estimate of the concentration corresponding to an excess lung cancer risk of 1% (i.e., URF = $1/EC_{001}$) consistent with the TCEQ (2012) guidelines.

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.

> **Response:** TCEQ agrees that the appropriate use of central estimates versus those at lower confidence intervals should be considered in all cases instead of simply relying on defaults. Relevant factors have been considered under TCEQ guidance (e.g., mortality versus incidence, meta-analysis approach), although not all may have been explicitly discussed in the DSD. Additionally, the central URF estimates utilized for the final value do not differ significantly from the upper estimates, the URFs are based on human data (see Reviewer #4 comments), and the desired degree of conservatism has been achieved. In regard to the nature of the estimates of exposure with which hazard levels are likely to be compared, although TCEQ does not consider this relevant to the determination at hand, the calculated air concentration at 1 in 100,000 excess risk is orders of magnitude higher than long-term CrVI ambient air levels monitored in Texas.

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.

> **Response:** TCEQ appreciates this positive feedback.

2.9 Calculation of the Final URF

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?

Reviewer #1: I would just use the 5 yr 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.

> **Response:** As the reviewer states, the difference between the optimal lag and 5-year lag for the Baltimore data is “imperceptible.” Since the optimal lag provides the best model fit, TCEQ believes this is most predictive and represents the best dose-response modeling, which is considered by TCEQ as more important than consistency in exposure lag time between the two key studies. However, text was added to the DSD to indicate that an identical final weighted URF would result from use of the 5-year lag URF for the Baltimore cohort.

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.

> **Response:** TCEQ appreciates this positive feedback.

Reviewer #3: Rationales for the choice of the URFs from each study appear to be based on 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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ did consider maintaining the same lag time (5 years) and minimum length of employment (1 year) between both cohorts. Reviewer #1 states the difference between the optimal lag and 5-year lag for the Baltimore data is "imperceptible." Since the optimal lag provides the best model fit, TCEQ believes this is most predictive and represents the best dose-response modeling, which is considered by TCEQ as more important than consistency in exposure lag time between the two key studies. However, text was added to the DSD to indicate that an identical final weighted URF would result from use of the 5-year lag URF for the Baltimore cohort.

2.10 Age-Dependent Adjustment Factors

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)?

Reviewer #1: Yes.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

Response: As indicated previously, additional text has been added to the DSD regarding considerations relevant to TCEQ's conclusion that a mutagenic MOA has not been adequately demonstrated.

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.

Response: TCEQ appreciates this positive feedback.

2.11 Meta-Analysis Approach

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 chronicESLnonthreshold(c)?

Reviewer #1: Yes it was appropriate to combine the two prefer URFs as done.

Response: TCEQ appreciates this positive feedback.

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 recipocal of the variance) is assigned to that estimate. This provides a better estimate of the URF and effect screening level (ESL).

Response: TCEQ appreciates this positive feedback.

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).

Response: As indicated in the draft DSD, variance in the β values used to derive the study-specific URFs reflects uncertainty in the β estimates, is a standard statistical procedure used in meta-analyses, and was used as an appropriate and objective weighting factor. Both of the study URFs utilized and their associated variances are very similar. Additionally, upper bound estimates of the URFs are not significantly different from central estimates. These facts are indicative of good inter-study agreement as well as relatively low uncertainty in the slope parameter values. Thus, whatever differences may exist between these studies potentially related to uncertainty, such differences ultimately

do not result in the studies providing appreciably different answers. The inverse-variance weighting resulted in a final URF of 2.28E-03 per µg/m^3 (rounded to 2.3E-03 per µg/m^3). Had any alternative weighting method been used, the final URF would have been between 1.94E-03 and 2.56E-03 per µg/m^3. That is, the final URF resulting from combining the two individual URFs for the Painesville and Baltimore studies cannot be more than 17.5% lower or 12% higher than the final URF calculated in the DSD using the inverse-variance weighting. This circumstance does not justify an attempted analysis of study uncertainty in an attempt to select just one study, which would be tantamount to discarding a large amount of highly relevant dose-response data by assigning one study a weight of 100%, and would likely be considered by TCEQ to be less objective (and transparently quantitative) than the weighting factor employed.

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.

Response: TCEQ appreciates the positive feedback in the first paragraph. In regard to the second paragraph comment on uncertainty associated with the Baltimore cohort study, whatever differences may exist between these studies potentially related to uncertainty, such differences ultimately do not result in studies providing appreciably different answers. Additionally, both the URFs and the weighting factors for the two studies are very similar. Use of variance in the β values used to derive the study-specific URFs as a weighting factor is an objective measure that takes into account the uncertainty and variability present in the epidemiological data, a standard statistical procedure used in meta-analyses, and is appropriate. In addition, any other weighting scheme would have resulted in a final URF that is between 1.94E-03 and 2.56E-03 per µg/m^3. That is, the final URF resulting from combining the two individual URFs for the Painesville and Baltimore studies cannot be more than 17.5% lower or 12% higher than the final URF calculated using the inverse-variance weighting. This circumstance does not justify a reevaluation or altering of the weighting procedure.

3. Other Questions

3.1 Uncertainty Analysis

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?

Reviewer #1: I think Appendix F presents a reasonable uncertainty analysis.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** TCEQ appreciates this positive feedback.

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.

> **Response:** As indicated in a previous response, both of the study URFs utilized and their associated variances are very similar, and upper bound estimates of the URFs are not significantly different from central estimates. These facts are indicative of good inter-study agreement as well as relatively low uncertainty in the slope parameter values. Thus, whatever the studies relative uncertainties may be, such differences ultimately do not result in appreciably different answers or significant consequence for the final URF. This circumstance does not justify an attempted analysis of study uncertainty beyond what is already presented in the DSD, which Reviewers #1 and #2 agree is a reasonable uncertainty analysis identifying key uncertainties and their impact on the URFs are adequately discussed.

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 TCEQ's assertion that background lung cancer rates are similar (or lessened) among these groups than among workers.

> **Response:** TCEQ appreciates the positive feedback in the first paragraph. In regard to the second paragraph comment on susceptibility and sensitivity, TCEQ agrees with the reviewer's comment that, "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…" Furthermore, TCEQ agrees with Reviewers #1 and #2 that the uncertainty analysis is reasonable, identifies key uncertainties, and adequately discusses their impact on the URFs.

3.2 Other Relevant Issues or Questions

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

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.

> **Response:** TCEQ appreciates the positive feedback. The mismatched table numbers were an artifact of omitting other sections not the subject of this review and have been corrected.

Reviewer #2: The Table numbers in the text do not match the actual Table numbers.

> **Response:** The mismatched table numbers were an artifact of omitting other sections not the subject of this review and have been corrected.

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.

> **Response:** The occupational-to-environmental concentration dosimetric adjustment in Section 4.2.3.1.5 is consistent with TCEQ guidance and a standard adjustment when using occupational data in a carcinogenic dose-response assessment. Because the exposure-response models used by TCEQ used cumulative exposure as the dose metric, the occupational-to-environmental dosimetric adjustments used in the CrVI DSD assumes that the dose metric is cumulative exposure to CrVI. This same occupational-to-environmental dosimetric adjustment would apply if average daily concentration had been used as the dose metric.

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.

> **Response:** TCEQ has previously determined, as outlined in guidance which underwent an external expert peer review organized by TERA, that it will not round numbers until the final toxicity factor is calculated. The final toxicity factor will be rounded to two significant figures, as has been historically done by TCEQ and was done in the DSD.

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 ug/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"

Section Number	Page Number	Comment
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?

Response: TCEQ appreciates the time required to develop these minor comments. Those which are highlighted (in gray) were addressed by TCEQ in the DSD. The last comment (regarding Table 2) is addressed in the following response. The expected number of lung cancer deaths (E) in Table 2 was back-calculated from the observed number of lung cancers (O) and the SMRs reported in Table 15 in Applied Epidemiology (2002). Cumulative exposure intervals to calculate SMRs can be defined using different criteria; for example: (a) intervals with approximately equal observed number of deaths in each group; (b) intervals with approximately equal expected number of deaths in each group; and (c) intervals with a convenient breakdown of the cumulative exposure, regardless of the number of observed and expected deaths in each group. The summary statistics given in Table 15 in Applied Epidemiology (2002) defined cumulative exposure intervals that were reasonable and that included at least some lung cancer deaths, regardless of the homogeneity in the observed and expected number of lung cancer deaths in the different groups.

4. Public Comments

The following addresses public written comments submitted by the City of Houston and the Ontario Ministry of the Environment and reported in Appendix C of TERA's June 17, 2013 expert panel review report.

4.1 City of Houston

Comment #1: Thank you for giving the Houston Department of Health & Human Services, Bureau of Pollution Control & Prevention 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 $\mu g/m^3$. The deadline for filing comments in May 24, 2013. The Houston Department of Health, Bureau of Pollution Control & Prevention endorses this change with the following comments.

Response: TCEQ appreciates the City of Houston's support for the draft carcinogenicity-

based ESL, which TCEQ believes is based on the most scientifically-defensible dose-response assessment possible.

Comment #2: 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[1] and as recently as 2012 it has been found in the ambient air downwind of some metal recycler facilities at unhealthy levels.[2] 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.

Response: The City of Houston's comment is noted. However, the technical and scientific merit of TCEQ's draft carcinogenic assessment of CrVI, as opposed to CrVI monitoring in TCEQ Region 12, was the subject of the external expert panel review and request for public comments (http://www.tera.org/Peer/crvi/index.html).

Comment #3: 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.

Response: This issue will be revisited by TCEQ as relevant data become available.

Comment #4: 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.

Response: This comment on TCEQ's policy-based, risk management excess risk level of 1 in 100,000 is noted. The no significant excess risk level for a carcinogenic chemical with a nonthreshold assessment such as CrVI is defined as the concentration associated with a theoretical excess lifetime cancer risk of 1 in 100,000. This theoretical excess lifetime cancer risk level is consistent with the State of California's No Significant Risk Level (22 CCR §12703) and is ten times less than the upper end of USEPA's acceptable risk range (1 in 10,000). This risk management goal was approved by the Commissioners and Executive Director of the TCEQ and is consistent with other TCEQ programs.

Footnote 1: 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

Footnote 2: Raun, Loren, Karl Pepple, Dan Hoyt, Arturo Blanco, Don Richner and Jiao Li. Community scale air pollution area sources and public health: Assessing risk from an under-regulated area source of metal particulate, Environmental Impact Assessment Review, April 2013.

4.2 Ontario Ministry of the Environment

Comment #1: I felt that much of the MOA section lacks sufficient supporting evidence and raises questions. For example:

Excerpt	Comment and Response to 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?) **Response:** Additional discussion and clarifying language relevant to the referenced excerpt was added to the MOA section of the DSD pursuant to the comment, consistent with its purpose for the document. A linear low-dose extrapolation was used as a conservative default in the absence of an adequately supported alternate approach with an acceptable level of scientific uncertainty for the protection of public health.
"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. **Response:** Additional text was added to the DSD pursuant to the comment.
"These MOA concepts are consistent with ATSDR (2012) indicating that CrVI absorption 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	As reviewed by Harvey Clewell for OSHA (2006) cell uptake will occur concurrently 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. **Response:** Additional discussion and clarifying language was

Excerpt	Comment and Response to Comment
(Thompson et al. 2011)."	added to the MOA section of the DSD pursuant to the comment.

Comment #2: 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.

> **Response:** Additional discussion and clarifying language was added to the MOA section of the DSD pursuant to the first part of the comment, consistent with its purpose for the document. TCEQ appreciates the positive feedback in the last part of the comment on the TCEQ decision to apply the URF to all forms of CrVI.

Comment #3: 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.

> **Response:** Additional discussion and clarifying language was added to the MOA section of the DSD pursuant to the comment, consistent with its purpose for the document. "A reasonably scientifically-rigorous standard for demonstration of a mutagenic MOA" refers to the evaluation under TCEQ guidelines of MOA analyses (or similar studies) published in the peer-reviewed literature which purport to demonstrate a mutagenic MOA.

Comment #4: 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).

> **Response:** TCEQ agrees that linear extrapolation is the most appropriate option at this time and believes that the approach in Haney et al. is associated with an unacceptable level of uncertainty utilizing currently available data.

5. References

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

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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, 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.

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