Scientific Peer-Review of the Carcinogenic Section (Section 4.2) of the Hexavalent Chromium Development Support Document Review Guidelines

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.

Due Date - Your written review should be returned to patterson@tera.org by email no later than May 24, 2013.

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.**