Scientific Peer-Review of the Carcinogenic Section (Section 4.2) of the Isoprene 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.

Your written review should be returned to nance@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 Isoprene. The draft DSD includes Section 4.2, which documents the derivation of an inhalation unit risk factor (URF) based on liver carcinoma incidence in mice and air concentrations corresponding to the policy-based 1 in 100,000 excess risk level. 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).

We are asking you to provide a review of the scientific approaches used by TCEQ in developing the URF for isoprene as described in the Carcinogenic Potential (Section 4.2) of the draft DSD. Information on the metabolism of isoprene is provided in Section 3.1.3 as additional background information for your review, but you are not being asked to review this section. 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 Ann Parker (parker@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

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. 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 Isoprene 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 4.2.3 briefly presents carcinogenic weight of evidence classification information and conclusions of authoritative bodies and TCEQ's weight of evidence conclusion. Is TCEQ's weight of evidence conclusion appropriate?**

5. **Section 4.2.4 discusses isoprene's carcinogenic mode of action (MOA). Have the authors clearly and accurately summarized the available data and hypotheses for isoprene's mode of action? [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. Ultimately, 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.]**

6. **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. **Were the most appropriate studies (Melnick et al., 1994a; Melnick et al., 1999; and Placke et al., 1996) selected for the dose-response assessment and was their selection sufficiently described and justified?**

    b. **Adjustments were made to the data to account for differences between the exposure durations and times of response observation, continuous exposure duration, and number of study animals, (Section 4.2.6.1). Are these adjustments biologically appropriate? Were the correct approaches used to adjust the data for each?**

    c. **Hepatocellular carcinoma, alveolar/bronchiolar carcinoma, and histiocytic sarcoma were selected as human-relevant cancer endpoints for the dose-response assessment. Was the selection of these endpoints clearly explained and justified? Do you agree with what was chosen?**

    d. **Benchmark dose modeling was conducted on the adjusted data for the endpoints identified, with the EC_{10} calculated for each cancer stage (m = 1, 2, 3). Was it appropriate to base the final URF on the number of stages with the lowest EC10? Do you agree with the selection of the best estimate, EC_{10}, (e.g., rather than the lower bound of the estimate, the LEC_{10}) as the point of departure (POD), and did TCEQ authors provide sufficient justification for this selection?**

e. **Were the analyses in the Appendix on the data for the critical effects correctly performed and were the conclusions adequately justified?**

7. **Did the dosimetric adjustments and conversion into human equivalent concentrations follow TCEQ guidance (Section 4.2.6.3)?**

8. **The final URF was derived using a non-threshold approach using the best estimate excess cancer risk resulting from continuous exposure to isoprene at 1 ppb in air for each cancer stage and then selecting the most conservative EC_{10} (cancer stage m=1) for use in deriving the ESL. Was this appropriate and does it result in the most appropriate URF and $^{chronic}ESL_{nonthreshold(c)}$?**

9. **Did the document provide sufficient justification for the decision that isoprene has not been demonstrated to have a mutagenic MOA for liver carcinogenicity?**

10. **Was the decision not to apply age-dependent adjustment factors (ADAFs) (Section 4.2.7) 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)?**

11. **Section 4.2.8 presents an uncertainty analysis. Have all the key uncertainties been identified? Are the conclusions regarding these uncertainty issues and their impact on the URF correct and sufficiently discussed?**

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