Peer Review of TCEQ Toxicity Factors Guidelines
Mode of Action and Epidemiology Issues

Introduction

In 2006, the Toxicology Division (TD) of the Chief Engineer's Office released a technical guide (RG-442) used by the Texas Commission on Environmental Quality (TCEQ) to develop Effects Screening Levels (ESLs), inhalation Reference Values (ReVs), and inhalation Unit Risk Factors (URFs). Although this document was primarily written as guidance for the TCEQ staff, it also documented the processes used to develop ESLs, ReVs, and URFs for any interested person with training in inhalation toxicology and risk assessment. ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, the potential for odors to be a nuisance, and effects on vegetation, while long-term ESLs are based on data concerning chronic health and vegetation effects. Welfare-based ESLs (odor and vegetation) are set based on effect threshold concentrations. Health-based ESLs, however, are calculated from ReV and URF toxicity factors. ReVs and URFs are based on the most sensitive adverse health effect relevant to humans. Derivation of a ReV or URF begins with a toxicity assessment involving hazard identification and dose-response assessment based on the chemical's mode of action. The resulting ReVs and URFs are then used to calculate ESLs that correspond to no significant risk levels.

The Texas Clean Air Act (Chapter 382 of the Texas Health and Safety Code (THSC)) specifically mandates the TCEQ to conduct air permit reviews of all new and modified facilities to ensure that the operation of a proposed facility will not cause or contribute to a condition of air pollution. Because of the comprehensiveness of the language in the THSC, the methods were developed so that ESLs could be derived for as many air contaminants as possible, even for chemicals with limited toxicity data.

Since 2006, new scientific developments in toxicology and risk assessment have resulted in changes to some risk assessment approaches, and the TD has derived some ReVs and ESLs through methods not specifically discussed in (but consistent with) the existing guidance (http://www.tceq.texas.gov/toxicology/dsd/final.html). As a result, the TD has prepared revised guidelines that will be entitled "Guidelines to Develop Inhalation and Oral Cancer and Non-Cancer Toxicity Factors." The Guidelines are presented in seven chapters. In Chapter 1, several fundamental topics are addressed including legal authority and regulatory use, consideration of cumulative risk, problem formulation, and public participation opportunities. Chapter 1 also provides an introduction to the different toxicity values and their use in calculating health-based inhalation ESLs, introduces and explains the use of Air Monitoring Comparison Values (AMCVs), and the use of toxicity factors in remediation projects. Chapter 2 describes how welfare-based ESLs are determined (i.e., odor- and vegetation-based values). Chapter 3 discusses common procedures used to develop both acute and chronic toxicity values for the inhalation routes and chronic toxicity factors for the oral routes of exposure. Chapter 4 addresses the procedures that are unique to the derivation of acute inhalation ReVs, and Chapter 5 addresses the procedures that are unique to the derivation of chronic toxicity factors. Chapter 6 provides procedures for the treatment of chemical groups and mixtures and Chapter 7 discusses procedures for using epidemiology studies to develop toxicity factors.

General Guidance to Reviewers

Reviewers are asked to consider all aspects of the methodology and evaluate strengths and weaknesses of the methods based on the specific questions described below, keeping in mind that TCEQ may need to develop toxicity factors even when there may be a less-than-desirable level of data in a chemical's database. Where possible, try to put the strengths and weaknesses in perspective by indicating their relative magnitude. Reviewers are asked to avoid emphasizing minor technical details or making tutorial comments. Reviewers should identify scientific uncertainties and suggest ways to reduce or eliminate those uncertainties.

For the evaluation of mode of action and use of epidemiology data, the reviewers will mainly review Chapters 3, 5 and 7. In particular, the reviewers are asked to focus on the consideration of the differences between children and adults when assessing risk and Chapter 7, which is a significant new revision since the 2006 document.

Charge Questions

<u>General Issues</u>

1. Does the guidance reference the most current, valid, and generally accepted federal or state guidance documents or key papers (Section 3.1)?

2. Are the procedures for addressing the differences between children's and adult's susceptibility to risk (Chapters 3 and 5) appropriate and consistent with accepted risk assessment methods? Procedures for addressing children's risk are found throughout the different sections of Chapters 3 and 5. In particular consider the following specific recommendations:
   - The definition of child as conception to 18 years of age
   - The definitions of susceptible, sensitive, and vulnerable
   - The identification of critical lifestages
   - The discussion of toxicokinetic and toxicodynamic differences between children and adults
   - The guidelines on how to identify studies that describe these differences

3. Does the guidance clearly describe the approaches to be used by TCEQ, and provide supporting rationale, in situations where it employed different procedures than those recommended in referenced federal or state guidance documents?

<u>Specific Issues for Evaluating Mode Of Action (MOA)</u>

4. TCEQ follows current U.S. EPA cancer guidelines for hazard identification, mode-of-action analysis and dose-response assessment for developing inhalation URF and oral SFo values (Chapter 5). Is this appropriate, or would other guidance be more appropriate?

Is TCEQ interpreting and applying the guidance correctly? If not, what changes to the methods would you suggest?

5. Chapter 3 (Section 3.5) and Chapter 5 (Section 5.7) describes the general process that TCEQ will follow to conduct an MOA analysis. Is this process complete, accurate, and consistent with accepted risk assessment practices?

6. Are the definitions of genotoxicity and mutagenicity used in the guidelines and adopted from McCarroll et al. (2010) appropriate in the context of discussing a mutagenic MOA evaluation? Are all major and relevant considerations (or key steps) included and put into appropriate context in weight of evidence approach for chemical carcinogenicity via mutagenic MOA? If possible, please help identify endpoints already included in the guidelines as genotoxic or mutagenic and provide other relevant input.

7. Please comment on any issues relate to mode of action analysis that have not already been addressed.

<u>Specific Issues for Hazard Characterization and Exposure-Response Assessment Using Epidemiology Data</u>

8. The major topics covered in Chapter 7 are listed below. Are there additional important topics that should have been discussed in these guidelines? Should any of these topics have been covered in more depth (keeping in mind that the Guidelines mainly present summary information with references to key documents that contain additional information)?
   7.4 Endpoint Selection
   7.5 Exposure Characterization
   7.6 Exposure Metric
   7.7 Dose-Response Models
   7.8 Quantitative Cancer Exposure-Response Characterizations
   7.9 Excess Risk Calculations for the General Population
   7.10 Determination of URFs and SFo Values from Dose-Response Modeling
   7.11 Meta-Analyses
   7.12 Reality Checks
   7.13 Uncertainty Analysis

9. Should the discussion of endpoint Selection (Section 7.4) include any additional pitfalls associated with using certain types of endpoints for risk assessment?

10. Should the discussion of Exposure Characterization (Section 7.5), include additional issues (e.g., temporality, measurements, models, reasonableness of underlying modeling assumptions, exposure estimation errors, grouped versus individual exposure values, and biomonitoring) associated with using certain types of exposure characterizations for risk assessment? Should the discussion of industrial hygiene measurements be expanded and, if so, how?

11. Should the guidelines have discussed additional exposure metrics (Section 7.6) or discussed additional issues related to cumulative exposure metrics (e.g., cumulative ppm-years)? Is the discussion of the advantages and disadvantages of using transformed exposure values as the exposure metric for exposure-response modeling complete? Are there additional issues and/or references relating to including more than one exposure variable (e.g., a second characterization of the exposure to the primary chemical, exposures to other chemicals) that should have been cited?

12. Is the discussion of dose-Response Models (Section 7.7) used in epidemiology studies complete or should have additional classes of dose-response models been discussed? Does the document accurately and completely present the issues/pitfalls associated with dose-response modeling based on reported summary characterizations (e.g., SMRs, RRs, ORs)?

13. The guidelines recommend using best estimates (e.g., maximum likelihood estimates) as the basis for comparing the exposure-response of two chemicals (Section 7.8). Is this recommendation consistent with accepted risk assessment practices? Is the recommendation clearly explained and well supported by the available references? Has the document completely discussed the issues/pitfalls/references associated with using bounds (e.g., 95% LCL, 95% UCL) as the basis for points of departure (PODs)?

14. Is the discussion of excess risk calculations (Section 7.9) complete? Would you recommend adding discussion of unidentified issues/pitfalls related to the calculation of excess risks for a specified general population (e.g., the Texas population) based on the dose-response modeling for the population (e.g., workers) in the epidemiology study?

15. Do the Guidelines clearly explain how TCEQ will determine whether to use linear or nonlinear dose-response models to develop URFs and SFo values (Section 7.10)? Are the recommended practices consistent with accepted risk assessment practices and completely supported by the available references? Should the document include any additional issues/pitfalls/references related to the choice between linear and nonlinear extrapolation below points of departure (PODs)?

16. TCEQ provides recommendations for how to determine the appropriate choice of the risk level (e.g., 1-in-a-thousand, 1-in-ten-thousand, 1-in-a-hundred-thousand, 1-in-a-million) for estimating the point of departure using linear low dose extrapolation (Section 7.10). Are these recommendations complete and consistent with accepted risk assessment practices? Please suggest any additional issues/pitfalls/references that should be added to the document.

17. Is the discussion of the general approaches to quantitative meta-analyses (Section 7.1), including discussion of combining risk measures, slope estimates, or data sets, complete? Please suggest any unidentified issues/pitfalls related to quantitative meta-analyses that should have been discussed.

18. In Section 7.12 (Reality Checks), TCEQ discusses the steps that can be used to at least partially evaluate the reasonableness of dose-response modeling assumptions and resulting estimates and bounds. Is this discussion complete, or are there additional approaches to reality checks that the TCEQ should be aware of? Can you recommend additional guidance concerning how the TCEQ should incorporate/utilize reality checks in its Development Support Documents (DSDs)?

19. Is the discussion of uncertainty analysis (Section 7.13) complete? Please suggest and additional general uncertainty analyses that the TCEQ should consider or any additional guidance concerning how the TCEQ should incorporate/utilize quantitative uncertainty analyses in its Development Support Documents (DSDs)?

20. Chapter 7 of the revised Guidelines includes the following appendices. Please comment on the usefulness of these appendices for illustrating the principals discussed in Chapter 7.
    - Appendix A: Linear Multiplicative Relative Risk Models
    - Appendix B: Example of a Meta-Analysis of Arsenic Cancer Dose Response Models Based on Published Summary Data

21. Please comment on any other issues related to using epidemiology data for hazard and exposure-response characterization that have not already been addressed.