Peer Review of TCEQ Guidelines for Derivation of Chronic Oral Toxicity Factors (noncancer and cancer)

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 chronic oral toxicity factors, the reviewers will mainly review Chapters 3 and 5. In particular, the reviewers are asked to focus on the significant revisions made since the 2006 document, additional consideration of the differences between children and adults when assessing risk, identification of health-based effect levels, additional guidance on how to determine if an effect is adverse, and development of oral reference dose (RfD) and oral cancer slope factor (SFo) values.

Charge Questions

General Issues

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?

4. Are the recommendations for determining adverse from non-adverse effects and the approach to determining if a response in a toxicology study is adverse or non-adverse appropriate and consistent with accepted risk assessment practices (Section 3.7.1)?

5. Section 3.7.1.4 provides a list of effects classified as not adverse, less serious, transitional, or serious. Do you agree with this classification of effects? Would you move any effect to different category or add an effect to any category?

6. In Chapter 3, are the general approaches described for identifying critical effect, selecting a key study, or defining the point of departure (including the hierarchy for selecting a point of departure) consistent with accepted risk assessment methodologies?

7. Should the critical effect be selected before or after uncertainty factors are applied (Section 3.11)?

8. Is the general information including cutoffs and definitions on physical/chemical properties described in Section 3.4.1 complete and appropriate?

9. When a free standing NOAEL is used as the POD, are exposure duration adjustments in Section 3.9.3 appropriate?

<u>Specific Issues for Oral Cancer and Noncancer</u>

10. Is the list of sources for published chronic oral toxicity factors (both RfD and SFo values) complete? (Chapter 5, Section 5.1).

11. Are dosimetric adjustments for oral cancer and noncancer appropriate? (Section 3.9, 5.2.2 and 5.3)
    - Adjustment of human and animal data to mg/kg-day
    - Interspecies scaling for cancer and non-cancer effects

12. Have all of the appropriate uncertainty factors been considered [Sections 3.12 and 5.5]? Would you make recommendations for a different approach to uncertainty factors? In particular, focus on the following issues that have been updated in the revised guidelines:
    - Accounting for differences between children and adult risk susceptibility in choice of UF_H and UF_D
    - Choice of different values (other than 1, 3, or 10) for UF_L
    - Choice of different values (other than 1, 3, or 10) for UF_D
    - UF_{Sub}

13. Is the definition of a minimum database for developing a chronic toxicity factor adequate? In particular, is the discussion of having adequate studies to evaluate children risk differences (Table 5-2; Sections 5.4 and 5.5) complete?

14. The revised guidance discusses several approaches for developing an RfD for chemicals with limited data. For each approach, please discuss whether the approach is applied correctly and appropriate for developing chronic RfDs in the absence of data.
    - Route-to-route extrapolation (Section 3.16 and Subsection 3.16.1)
    - Relative potency (Section 3.16 and Subsection 3.16.2)

- Use of LD_{50} (Section 5.6)

15. Are there other issues specific to developing chronic oral toxicity factors that have not been adequately addressed in the document?