Texas Commission on Environmental Quality
Responses to Peer Review Report

May 31, 2006

Texas Commission on Environmental Quality
Toxicology Section
Chief Engineer's Office

Prepared by:

Toxicology Section
Chief Engineer's Office

COMMENTS FROM PANEL MEMBERS AND THE PUBLIC

The October 12, 2005 *Report of the Peer Review Meeting on Development of Effects Screening Levels, Reference Values, and Unit Risk Factors for the Texas Commission on Environmental Quality* (TERA 2005) (hereafter referred to as the Peer Review Report) is available on the following TERA website: http://www.tera.org/peer/TCEQ/TCEQWelcome.htm.

The Toxicology Section (TS) of the Texas Commission on Environmental Quality (TCEQ) has prepared responses to comments from panel members and the public. The TS would like to thank the peer review panel for their careful review of the initial ESL Methodology document and their constructive suggestions. The great majority of the panel member and public comments have been incorporated into the revised Public Comment Draft of the ESL Guidelines document. Panel member comments contained in Section 6 *Summary* of the Peer Review Report have been addressed first, since these comments represent consensus opinions concerning the most significant changes to the ESL Guidelines. Similar comments that were recorded multiple times have been addressed only once in order to avoid needless repetition of the same issues. Comments from the public and other interested parties are then addressed.

6. Summary

1. Comment Page 33: Overall, the panel concluded that the document incorporates the most current and relevant federal and state guidance. However, the document should not only focus on the US guidance but should also incorporate international guidance such as OECD, IARC, and WHO.
   Response: Additional references to guidance produced by some of these international organizations have been included in the revised ESL Guidelines, as well as a brief acknowledgement and reference to organizations from other countries that conduct toxicity assessment, although no attempt has been made to produce an exhaustive list. The purpose of the ESL Guidelines is not to provide a world-wide view of toxicological principles, especially if principles of risk assessment are adequately presented in current USEPA documents and scientific articles that are referenced in the ESL Guidelines. In addition, state legislative authority indicates that USEPA methods should be followed.

2. Comment Page 34: The panel suggested that the criteria for selecting data sources for chemical-specific values should include peer review and public involvement. For acute values, panel members suggested that STELs and ceiling values were more relevant than IDLH values. Panel members also suggested that the terminology used to describe acute studies be made consistent with standard inhalation toxicology practice.
   Response: Suggestions made by the panel members have been incorporated.

3. Comment Page 34: For chronic values, the panel suggested that other countries' agencies such as Health Canada or RIVM be included. They also suggested that values from ATSDR and CalEPA be given higher priority than EPA's PPRTVs and HEAST because these values have some external peer review and public involvement. Finally, the panel suggested that occupational values that are strictly health-based, such as TLVs, are the more appropriate source for environmental risk assessment.
   Response: Suggestions made by the panel members have been incorporated. In addition, see response to panel comment #1.

4. Comment Page 34: In spite of the discussion of data sources for existing risk values, the panel recommended that the document place more emphasis on evaluating the available data for chemicals. The panel suggested that TCEQ should critically evaluate the data and assumptions underlying an existing value and ensure that it is consistent with TCEQ's objectives before adopting the value. The panel also suggested that TCEQ apply the following analytical approach as the foundation of the ESL document, which would apply to both evaluation of ready made values and data sets for which no values are available.

   - Review the underlying data
   - Describe expectations for chemical toxicity based on physical and chemical characteristics e.g., does this chemical have properties that indicate it is likely to be reactive in the portal of entry (POE)
   - Conduct a mode of action analysis that describes in detail the potential for toxicity and the nature of the dose response curve
   - Choose the appropriate dose metric
   - Conduct appropriate dosimetric modeling
   - Select critical effect and point of departure
   - Apply appropriate uncertainty factors.

   Response: Suggestions made by the panel members have been incorporated in Chapter 2.

5. Comment Page 34: The panel suggested that for each key decision point in the document, TCEQ should describe the criteria that will be used to make the decision and the data needed to move away from default assumptions. The panel felt that since the ESL document encourages the use of professional judgment, it is important to describe how professional judgment should be exercised.
   Response: Criteria and examples have been included throughout the ESL Guidelines to provide guidance on the use of professional judgment.

6. Comment Pages 34-35: The panel made several suggestions regarding the selection of the critical effect and point of departure:

   - Following EPA guidance, choose the appropriate dose metric and conduct dosimetric modeling **before** selecting critical effect and POD,
   - Select species and effect most relevant to humans, not necessarily the most sensitive. Choosing the most sensitive species is the default only when data regarding relevance to humans are missing.
   - The most appropriate choice for selecting the point of departure is one that fits data using a mathematical model, such as benchmark modeling. Using a NOAEL is the weakest approach for a POD.
   - Consider severity in selecting the POD.

   Response: Suggestions made by the panel members have been incorporated in Chapter 2.

7. Comment Page 35: In evaluating the approach to cancer assessment, the panel suggested that the document acknowledge that the outcome of a cancer assessment can be either a linear or nonlinear dose response assessment, depending on the chemical's mode of action. The panel emphasized again that by following the analytical framework suggested above, the document will more closely follow the cancer guidelines, because it is critical to understand the mode of action in order to select the appropriate dose response assessment for each chemical. Following this analytical framework will also lead to harmonized cancer and noncancer assessments.
   Response: Chapters 1 and 2 have been revised to present a harmonized cancer and noncancer assessment. Figure 2 has been revised.

8. Comment Page 35: The panel made the following suggestions regarding dosimetry:

   - The treatment of Haber's Law and duration adjustments is outdated and several new publications should be incorporated to bring it up to date.
   - The discussion of Haber's Law should be incorporated into the body of the text, rather than in an appendix.
   - The more general power law equation (i.e., $C^nT=K$ or $C^nT^m=K$, depending on the richness of the data sets for a particular endpoint) should be used rather than Haber's Law as this law has been shown to be a special case of the power law family of curves.
   - Even if the general power law equation is used to fit the experimental data, there are significant problems in extrapolating beyond the range of the data. For example, it is not appropriate to use exposures longer than about 8 hours to adjust to a one hour exposure scenario.
   - The document should clarify whether particle dosimetry is being conducted to allow for interspecies extrapolation or to evaluate whether experimental exposures are relevant to human exposures.
   - The document should clarify what particle diameter is being used for expression of particle exposures.
   - The document should recognize that the dosimetric approaches recommended for chronic exposures can also be applied to acute exposures, with the exception that different dose metrics may be appropriate for acute exposures than chronic exposures.

   Response: Suggestions made by the panel members have been incorporated in Chapter 2.

9. Comment Page 35: When considering chemicals with limited data sets, the panel suggested that the three approaches discussed in the document should be considered as providing supporting information only. The panel suggested that the best approach to limited data may be to apply a default "generic" ESL rather than developing a chemical-specific ESL with unreasonably large amount of uncertainty.
   Response: Suggestions made by the panel members have been incorporated in Section 3.5 *Chemicals with Limited Toxicity Data.*

10. Comment Page 35: The document needs to define the minimum database needed to develop low- and high-confidence acute and chronic ESLs so that it can describe procedures to use when data are inadequate or when specific data are missing.
    Response: Suggestions made by the panel members have been incorporated in Section 3.3 *Minimum Database for Development of an Acute ReV* and Section 4.3 *Minimum Database for the Development of a Chronic ReV.*

11. Comment Page 35: Describe the tools that will be used to evaluate structure activity relationship and define the criteria that will be used to assess similarity of structure.
    Response: Structure activity relationships and toxicity information on chemical classes are being used as supporting information only. Refer to Section 3.5.3 *Tier III – Relative Toxicity/Relative Potency Approach*.

12. Comment Page 36: Applying the ratio of LD_{50}s is not recommended for assessing inhalation exposures.
    Response: This section has been removed from the revised ESL Guidelines. Refer to Section 3.5 *Chemicals with Limited Toxicity Data.*

13. Comment Page 36: The "dose conversion" equation described for conducting oral to inhalation extrapolation is not appropriate. If a route-to-route extrapolation must be conducted, equations from recent papers (Overton, 1990; Overton and Jarabek, 1989a,b) give better default parameters than the dose conversion.
    Response: Suggestions made by the panel members have been incorporated in Section 2.1.3.

14. Comment Page 36: If route-to-route extrapolation is used, consider applying an additional UF.
    Response: Route-to-route extrapolation will be considered only if strict criteria are met. If route-to-route extrapolation is used, the TS will consider applying an additional incomplete database UF.

15. Comment Page 36: Overall, the panel agreed with the approach to uncertainty factors taken in the document, but suggested that the document should more clearly describe the intent to replace default UFs with actual data, if available. In addition, the document should distinguish between the factors that describe variability and those that describe a lack of knowledge. The document should acknowledge that the factors describing variability are both composed of kinetic and dynamic subfactors.
    Response: Suggestions made by the panel members have been incorporated in Section 2.11 *Apply Appropriate Uncertainty Factors for Chemicals with a Nonlinear Dose Response.*

16. Comment Page 36: Consider only modeling benchmark responses of minimal severity before determining whether an uncertainty factor for LOAEL to NOAEL extrapolation is needed.
    Response: Suggestions made by the panel members have been incorporated in Section 2.6 *Determine the POD.*

17. Comment Page 36: Apply an UF if an LC_{50} is used as the basis of an acute ESL.
    Response: Refer to Section 3.5 *Chemicals with Limited Toxicity Data.*

18. Comment Page 36: The panel suggested that the document should distinguish between cumulative risk and aggregate risk. The approach followed for addressing cumulative/aggregate risk does not follow accepted risk assessment methods; although using a hazard quotient of 0.1 as a screening tool has been done by some federal and state programs. If screening air permits is the only objective then using an HQ of 0.1 is likely adequate. But if TCEQ has risk management objectives that require a more "detailed" risk value, then an approach that considers adding risk according to target organ, mode of action, or chemical class would be more appropriate.
    Response: The section on cumulative risk has been revised to distinguish between cumulative risk and aggregate risk and to reference an appropriate guidance document. A risk management section has been included in Chapter 1. For evaluating air permit applications, a screening approach using ESLs is the objective. For evaluating air monitoring data, ReVs and URFs are used. Measured ambient concentrations represent the aggregate influence of multiple sources. When the TCEQ uses ReVs and URFs to assess cumulative risk, it will consider adding risk according to target organ, mode of action, or chemical class.

19. Comment Page 36: The document should develop HQs for the noncancer properties of carcinogens and consider them in the cumulative risk assessment.
    Response: It was always the intent of the ESL Guidelines to develop toxicity factors based on the noncancer properties of carcinogens, if there is adequate toxicity information on the noncancer properties of those carcinogens. These toxicity factors could be either ReVs or URFs, depending on the nonlinearity/linearity of the dose response. Long-term ESLs (which are used in air permitting) are the lower of the following health-based ESLs: ${}^{Chronic}ESL_{Nonlinear(nc)}$, ${}^{Chronic}ESL_{Linear(nc)}$, ${}^{Chronic}ESL_{Nonlinear(c)}$ or ${}^{Chronic}ESL_{Linear(c)}$.

20. Comment Page 36: When describing the chemicals that are exempt from ESL development, the document should describe the criteria that are used for including a chemical on the exempt list as well as the criteria that would be used to remove a chemical from the list.
Response: Criteria for including and removing chemicals from the exempt list are provided in Chapter 1. The TS has added additional information to Appendix D as suggested.

21. Comment Page 36: In addition, if chemicals are on the exempt list because they are regulated by another program, then the document should state this and describe which program regulates the chemical.
Response: Currently, there are no chemicals on the Exempt list that are affected by this comment. In the future, suggestions made by the panel members will be incorporated as applicable.

22. Comment Page 36: The panel suggested that the choice of a 50% odor threshold for setting the odor ESL should be better explained in the document because the ability to perceive odor does not necessarily correlate with concentrations associated with toxicity, and odor detection also involves cognitive issues not related to chemical concentration.
Response: We agree. The ESL Guidelines never suggests that the ability to perceive odor correlates with concentrations associated with toxicity. Health-based ESLs are developed for each chemical. An ESL based on odor potential is developed if adequate information is available. Both the health-based ESL and the odor-based ESL is presented in the derivation support document. The lowest concentration, whether based on odor potential, vegetative effects, or health, is set as the screening-level ESL. The TCEQ frequently receive complaints about odor problems, so an ESL that evaluates odor potential is an important consideration for welfare. No change to the ESL Guidelines is required.

23. Comment Page 36: The panel suggested that the potential for sensory irritation, as measured by the concentration that results in a 50% reduction in respiratory rate in rodents (the RD_{50}), would be a better basis for an ESL than odor.
Response: We disagree. If humans are exposed to concentrations at the RD_{50}, they experience significant discomfort and irritation. The RD_{50} is considered as supporting information for a health-based ESL, since sensory irritation to the eyes, nose, upper respiratory tract, etc. is considered a health effect. The concentrations where people perceive odor is different than concentrations corresponding to the RD_{50}. The TCEQ frequently receive complaints about odor problems, so an ESL that evaluates odor potential is an important consideration for welfare. No change to the ESL Guidelines is required.

24. Comment Page 37: Strengthen the document by using more graphics to illustrate key points. Flow charts need to be constructed so that they do not reach dead ends. The flow charts should be redrawn to more accurately reflect TCEQ's process. Figure 2 (chronic ESLs) should reflect the U.S. EPA cancer guidelines more closely and either add a pathway for nonlinear mode of action or allow the output of the cancer analysis to be either a URF or ReV for non-linear dose response.
Response: Suggestions made by the panel members have been incorporated.

25. Comment Page 37: Terminology - clarify and update terminology used in order to be more consistent with U.S. EPA guidelines.
Response: Suggestions made by the panel members have been incorporated.

26. Comment Page 37: Define "welfare" and consider including approaches from NAAQS that deal with welfare issues

Response: A discussion of welfare has been incorporated in the revised ESL Guidelines in Chapter 1. The definition of welfare effects from the NAAQS is not the same as the consideration of welfare effects authorized by the Texas Clean Air Act.

27. Comment Page 37: Reorganize the document so that all of the issues common to acute and chronic ESLs are placed in Chapter 2. For example move discussions about benchmark modeling, dosimetry, and uncertainty factors to Chapter 2. Then Chapters 3 and 4 can focus on issues that are unique to development of acute or chronic values.
    Response: Suggestions made by the panel members have been incorporated.

28. Comments on Pages 3-5: Executive Summary
    Response: Panel member comments in the Executive Summary were identical to comments in Section 6 *Summary* and have already been addressed.

Section 4.2 Clarifying Questions from the Panel

29. Comment Page 11: Panel members noted that the U.S. EPA NAAQS include ecological effects and that ozone, for example, has ecological effects down to background levels.
    Response: Ecological risk assessments are not conducted during the air permitting process.

30. Comment Page 11: However, since the public has input into the ESL values, the public also needs to understand how the ESLs are developed. To facilitate public understanding of the document, one panel member suggested that document include a "lay person" appendix.
    Response: A lay person pamphlet will be prepared to help the public understand how ESLs are developed. It will not be included in the ESL Guidelines. The *Document Description and Intended Use* of the ESL Guidelines clearly states "Although this document is primarily written as guidance for the TS staff, it also documents (largely by reference) the processes used to develop ESL, ReV, and URF for any interested person with training in inhalation toxicology and risk assessment."

31. Comment Page 11: Another person suggested that the document include more background on the permitting process and air monitoring to help the public understand how ESLs, ReVs, and URFs are used.
    Response: A lay person presentation on the permitting process, how air monitoring is conducted, and how ESLs, ReVs, and URFs are used will be prepared and posted on the TCEQ Toxicology Section website.

32. Comment Page 11: Another reviewer asked if TCEQ has a formal process for prioritizing which of the old ESLs will be revised first. TCEQ indicated that it will eventually develop new ESLs for all chemicals, but the priority will be based on professional judgment as to which chemicals most often are detected in ambient air monitoring or are most frequently seen in the permitting process.
    Response: The guidelines have been revised to describe the approach for prioritization of chemicals in Section 1.10 *Selection of Chemicals for ESL Development and Data Solicitation.*

4.3 Observer Presentation, Comment Pages 11-13

Response: Oral Comments made by Dr. Stuart Cagen of Shell Chemical Company and Mr. Evan Johnson of the group Public Citizen were similar to written comments submitted by the Texas Chemical Council and Dr. Neil Carmen of the Lone Star Chapter of the Sierra Club on behalf of several organizations including Public Citizen (Appendix E, Written Observer Comments) prior to the meeting. Therefore, only responses to written comments have been provided (Appendix E Written Observer Comments).

5.1 Data Sources

33. Comment Page 14: Panel members noted the following guidance that should be added: (1) discussion of the Categorical Regression software that was developed explicitly to address issues of acute data; (2) the cumulative & aggregate risk approaches developed in the Office of Pesticides and Toxic Substances at the U.S. EPA; (3) reference to the NAAQS and Ecological Risk Assessment guidance for evaluation of vegetation effects.
    Response: Guidelines for using Categorical Regression is an active, ongoing area of research. There are several outstanding issues/questions raised by the Science Advisory Board on the use of Categorical Regression that need to be addressed by USEPA, so the TS does not plan to use this technique at the present time. The TS will consider the use of Categorical Regression in the future.

    Since ecological risk assessments are not conducted during the air permitting process, the TS does not intend to reference the Ecological Risk Assessment guidance for evaluation of vegetation effects. The TS does not believe the NAAQS guidance provides generally applicable guidance for vegetation-based ESL development given the paucity of vegetation toxicity data. The TS will consider incorporation of additional guidance and data as they become available. Cumulative and aggregate risk considerations have been incorporated with reference to USEPA's Framework for Cumulative Risk Assessment.

34. Comment Page 14: Another panel member noted that US EPA, 2002, which is a review of the RfC methodology intended to be an agency-wide view of childhood issues, found that the RfC process adequately addressed childhood issues. However, other panel members remained unconvinced that standard risk assessment practices always adequately address all child uncertainties.
    Response: We agree with the panel member who noted that the RfC process adequately addresses childhood issues. For carcinogens, the ESL Guidelines incorporate guidance in the 2005 cancer guidelines to address potential increased susceptibility of children to carcinogens that work though a mutagenic mode of action.

35. Comment Page 14: For acute ESLs, panel members concluded that, overall, the list of sources seemed complete and the proposed hierarchy was appropriate. Except . . .
    Response: A hierarchy of ready-made acute toxicity factors has no longer been incorporated in the revised ESL Guidelines, although acute reference values available from different organizations are presented and discussed as a source of toxicity information for a chemical.

36. Comment Pages 14-15: One panel member noted that the document recommends using studies up to 4 weeks in duration for developing acute ESLs, and that this is different from other states.
    Response: The ESL Guidelines has been revised to (1) define the minimum database needed to develop an acute chemical-specific ESL; and (2) to establish an approach to derive generic ESLs if the minimum database requirements are not met. However, if the only defensible toxicity study on a chemical is a 4-week study, then the TS uses this study if the mode-of-action analysis indicates it is appropriate. Refer to Section 3.2.3 *Adjustments for Subacute Studies*.

5.2 Hierarchy of Risk Assessment Approach

37. Comment Pages 15-17: (including all comments made in section 5.2 Hierarchy of Risk Assessment Approach):
    Response: A hierarchy of ready-made acute and chronic toxicity factors will no longer be incorporated in the revised ESL Guidelines, although reference values available from different organizations will be presented and discussed as a source of toxicity information for a chemical. Suggestions made by the panel members in Section 5.2 have been incorporated, if appropriate, based on the new approach.

5.3 Criteria/Professional Judgment

38. Comment Page 18: One panel member suggested that the document needed criteria for when a peer review of a chemical-specific ESL was needed.
    Response: The guidelines have been revised to reflect criteria for when a peer review of a chemical-specific ESL will be conducted in Section 1.11 *Public Comment and Peer-Review*.

5.4 Critical Effects/Point of Departure

39. Comment Page 18: Several panel members suggested that field studies and occupational studies should be added to the list of acceptable human studies . . .
    Response: Field studies and occupational studies have been added to the list of acceptable human studies.

40. Comment Page 18: One reviewer disagreed with the statement made in the ESL document regarding causality and epidemiology studies. This reviewer noted that when evaluating studies by the Hill criteria, epidemiology studies are frequently insufficiently robust to identify or establish cause-effect relationships.
    Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

41. Comment Page 18: In addition, another panel member noted that the approaches do not seem to take into account the severity of effects, just the effects at the lowest dose. The approach must also address severity. TCEQ indicated that the goal of the methods was to select the most sensitive effect as the critical effect.
    Response: Section 2.10 *Extrapolate from the POD to Lower Exposures and Select Critical Effect* has been revised to address this issue.

42. Comment Page 18-19: Panel members replied that the methods should focus on the most relevant adverse effect to humans; evaluating the mode of action and focusing the risk assessment on the most relevant effect leads to harmonization of cancer and non-cancer risk assessment. Another panel member agreed and suggested that basing an assessment on precursor effects that occur at lower concentrations would result in a risk value that is also protective of cancer. The ESL document should clarify that the choice of most sensitive health effect is a precautionary procedure in the absence of definitive data regarding relevance to human disease outcomes.
    Response: Section 2.3.3.2 *Animal Data* has been revised to emphasize that a consideration of relevant adverse effect to humans should be considered and a sentence has been added that states choosing the most sensitive health effect observed in animals is a precautionary procedure in the absence of definitive data regarding relevance to human disease outcomes.

43. Comment Page 19: One panel member noted that the use of benchmark modeling is only discussed in the section on acute ESLs, but this approach is also used for developing chronic values. In fact, benchmark modeling is actually used more than the NOAEL/LOAEL approach for developing RfCs. Therefore, this panel member suggested moving this discussion to Chapter 2, Common Procedures, of the ESL document.
    Response: Benchmark dose modeling is discussed in Chapter 2 *Common Procedures Used to Derive Acute and Chronic Toxicity Factors*.

44. Comment Page 19: Another reviewer agreed, indicating that it is possible to manipulate experimental design to alter the LOAEL. Therefore, it is important to consider the power of the study to detect a NOAEL before selecting the POD. Other panel members agreed that BMC modeling is the best approach to estimating the POD and noted that there are very few situations where the data do not support BMC modeling. In evaluating the NOAEL/LOAEL bracket, the document should put more emphasis on the more severe effects. In conclusion, the panel suggested

that the most appropriate approach for selecting a point of departure is one that fits data to a mathematical model.
Response: We agree. In the original ESL Methodology, the section entitled *Point of Departure* states "When possible, the TS performs BMC modeling following established guidelines (USEPA 1995; USEPA 2000b) because of the advantages of this approach over the NOAEL/LOAEL approach." Therefore, no change in the ESL Guidelines is needed.

5.5 Cancer

45. Comment Page 19: One reviewer noted that there were some areas where the document does not follow the EPA 2005 cancer guidelines. For example the document does not address the hazard characterization step of risk assessment at all. In addition, the document needs to describe how to do a weight-of-evidence analysis based on a chemical's mode of action. The panel reiterated the analytical approach discussed in Section 5.2, Hierarchy, and noted that if the ESL document follows this type of analysis, it will be more consistent with the U.S. EPA's 2005 Cancer Guidelines.
Response: Chapter 2 of the ESL Guidelines has been revised to include the analytical approach recommended by panel members (refer to response #4). Section 4.5 *Linear Carcinogens and Nonlinear Carcinogens* has been revised.

46. Comment Page 19: The resulting analysis will have a more integrated cancer/non-cancer assessment. Another reviewer agreed, noting that noncancer endpoints can have linear dose-response relationships. Likewise, carcinogens can be nonlinear. Therefore it is important to understand mode of action in order to select the appropriate dose-response assessment. This reviewer noted that harmonized cancer/noncancer approaches have been proposed for some key chemicals.
Response: Chapters 1 and 2 have been revised to present a harmonized cancer/noncancer approach.

47. Comment Page 19: However, the first panel member pointed out that the 2005 Cancer Guidelines do not pay enough attention to the appropriate dose metric and dosimetry models to use for inhalation assessments, so it is important to incorporate guidance on these issues from other sources.
Response: Chapter 2 has been revised to include Section 2.5 *Choose the Appropriate Dose Metric* and Section 2.7 *Conduct Appropriate Dosimetric Modeling*. Section 4.5.3 *Dose-Response Assessment*, references the updated dosimetry sections in Chapter 2.

48. Comment Page 19: One reviewer noted that the term "mutagenic carcinogen" is imprecise because there are some chemicals that are both carcinogens and mutagens, but are not carcinogenic by a mutagenic mode of action. It would be more accurate to refer to carcinogens as "operating via a mutagenic mode of action".
Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

49. Comment Pages 19-20: This reviewer also noted an error in the guidelines that was carried through to the TCEQ document. On Comment Page 38, for time-weighted averaging, should be 14/70 and 54/70 - not 13/70 and 55/70.
Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

50. Comment Page 20: On Comment Page 34, line 33, the document states "...the 2005 Cancer Guidelines allow flexibility to depart from conservative default assumptions." However, this reviewer indicated that this is a misinterpretation of the 2005 guidelines. Rather, the guidelines

(see section 1.3.1 of 2005 EPA *Cancer Guidelines*) encourage risk assessors to evaluate the available data, and invoke defaults only when there are not data to support a better decision. On Comment Page 36, the bulleted list in Section 3.2.2.3 is not used correctly. This list presents options combining multiple risk estimated, for example from several different tumor types, not the procedure for combining linear and nonlinear estimates. Similarly, the list that appears on Comment Page 37 was not meant in the guidelines to be prescriptive, but rather to provide examples of the types of evidence that one may see in evaluating a mutagenic mode of action. The equations on Comment Page 38 presume a constant exposure concentration continuously over a lifetime and this presumption needs to be stated in the document.
Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

51. Comment Page 20: Panel members also discussed the approach to age adjustments for cancer analysis and quantitative assessment. One panel member indicated that the guidelines recommend a linear default as a conservative position when the mode of action is not known and age adjustments (age dependent adjustment factors) are used only when a mutagenic mode of actions has been determined. Vinyl chloride is an example of where the age dependent default adjustment factor (ADAF) is not applicable as chemical-specific data on early life susceptibility are available and were used by Agency in deriving the slope factors. Another reviewer suggested that it is better to incorporate mechanistic approaches and life-stage dosimetry than to use the ADAF. With respect to life stage considerations, several studies may be useful (Jarabek et al., 2005; Dietert et al., 2000; Clewell et al., 2004; Ginsberg et al., 2004).
Response: We agree with the panel members that for carcinogens operating via a mutagenic mode of action, an age adjustment should be applied to account for potential early life sensitivity.

52. Comment Page 20: Finally, reviewers noted that implementing the guidelines is difficult and suggested that TCEQ look at the chloroform assessment available on IRIS or the vinyl acetate assessment by Bogdanffy and Jarabek (1995)
Response: The panel suggested that more examples be included in the ESL Guidelines. A brief discussion and reference to the chloroform assessment and the vinyl chloride assessment have been included in the revised ESL Guidelines.

53. Comment Page 20: Another panel member noted that Section 2.4.2.1 of the 2005 cancer guidelines presents good discussion on how to evaluate and accept a mode of action.
Response: Section 2.4 of the 2005 Cancer Guidelines has been referenced in the section of the revised ESL Guidelines dealing with how to evaluate and accept a mode of action.

5.6 Dosimetry

5.6.1 Haber's Law

54. Comment Pages 20-21: One panel member agreed that PBPK modeling was the best approach to dosimetric adjustments; however, when PBPK models are not available, the document does not apply Haber's Law assumptions correctly. Generally, concentration is more important than time. Panel members agreed with the approach to include a chemical-specific "n" value into the equation; however, the method can be taken further by putting exponents on "C" and "T" too (see Miller et al., 2000). Another panel member noted that "n" values depend on where the inflection is located and on the type of data utilized to develop the empirical relationship.
Response: A brief discussion and reference to the Miller et al. 2000 paper discussing the generalized power law family function (i.e., $C^nT^m = K$) has been included in the revised ESL Guidelines. If experimental data is available to derive chemical-specific and endpoint-specific

exponents of “n” and “m” for both “C” and “T”, then this procedure will be followed. However, in the majority of cases, experimental data will not be available so default values of “n” as described in Section 2.8 *Default Exposure Duration Adjustments* will be used to perform duration adjustments.

55. Comment Page 21: One panel member noted that there are some errors in the appendix on Haber’s Law. First, in the plots on Comment Page 65, the C and T axes are reversed.

    Response: The majority of guidance documents and scientific papers that discuss Haber’s Law have time on the x-axis and concentration on the y-axis. No change to the ESL Guidelines is required.

56. Comment Page 21: The equation for Figure G-2 should be Log C^n + Log T = K', realizing that K' is really equal to Log K from the equation C^nT=K. Second, this panel member does not agree with the ways the document used to arrive at the different time points. The preferred approach is to have equal spacing on log scale and to span two orders of magnitude**.**

    Response: The equation in Figure 2-4B has been corrected. The figure is meant to illustrate the relationship of C^n x T = K for a 1-, 4-, 6-, 8-, and 24-hour exposure duration, for different values of “n” for a hypothetical case where experimental data are available for a two-hour exposure duration to an air concentration of 200 ppm. Figure 2-4B illustrates the linear relationship between log concentration versus log time for the data from Figure 2-4A. Therefore, the graph does not span two orders of magnitude.

57. Comment Page 21: Also, this panel member notes that the document uses an n=3 but actually, n should be greater than 3 - closer to 3.5, resulting in a more conservative ESL value. This approach would be better in situations where there are no data demonstrating the value of n. When data are available, those data should be used. One reviewer noted that the relationships described in the ten Berge and Miller papers are based on mortality, but that n is dependent on endpoint. Therefore, this reviewer was uncomfortable specifying a value for n based on mortality data.

    Response: This comment refers to Section A.2 Default Procedures of the original Methodology which states “However, when the exposure duration of the key study is greater than 8 hours and less than 4 weeks, “n “ is assigned a value of 3.” This sentence has been removed from the ESL Guidelines. Please refer to the Section 3.2.3 *Adjustments for Subacute Studies.*

58. Comment Page 21: One panel member noted that for very brief exposures, it would not be meaningful to adjust the duration to 1 hour, given the lack of data. One panel member asked if this meant that a 15 minute data was the same as 1 hour. The first reviewer replied that no, it is just the opposite - it is better to let the data set identify best value for “n” for concentration and “m” for time by fitting the data to the generalized power law family function (i.e., C^nT^m = K). For example, Miller and colleagues (2000**)** define situations when risk is being over or under predicted depending upon whether the region of interest is above or below the line of identity, which is the line defined by Haber’s Law. Another reviewer indicated that when extrapolating from a shorter to longer duration, n=1 should be assumed for C x T. Other panel members agreed, but indicated that this is not true if the chemical is accumulative or for developmental/reproductive toxicants. Therefore, it is important to look at the mechanism data for each chemical and determine the appropriate duration adjustment on a case-by-case basis.

    Response: We agree with the panel member who stated when extrapolating from a shorter to longer duration, n = 1 should be assumed for C^n x T. We also agree with the panel members who stated it is important to look at the mechanism data for each chemical and determine the appropriate duration adjustment on a case-by-case basis. If there is an experimental data set that

can identify a best value for "n" for concentration and "m" for time by fitting the data to the generalized power law family function (i.e., $C^nT^m = K$), this information will be used.

59. Comment Page 21: When extrapolating from a longer to shorter duration, one should use the concentration with no adjustment.

    Response: We agree. Refer to Sections 3.2.2 *Duration Adjustments from an Exposure Duration > 1 h to 1 h* and 3.2.3 *Adjustments for Subacute Studies*.

60. Comment Page 21: When extrapolating from 4-week data to a shorter time, using concentration is conservative.

    Response: We agree. Refer to Section 3.2.3 *Adjustments for Subacute Studies*.

61. Comment Page 21: One reviewer stated that C x T does not apply for odor or irritation. Other reviewers agreed and indicated the importance of understanding the biology and how it is affected by C x T.

    Response: We agree. Section3.2 *Acute Exposure Duration Adjustments* discusses this concept and clearly states that exposure duration adjustments for odor or mild sensory effects will not be conducted unless experimental data suggest odors or mild sensory effects increase in severity because of the cumulative dose over time.

62. Comment Page 21: Another panel member indicated the relationship is only useful over a limited time extrapolation. For example, one should never use an extrapolation from a study longer than 8 hours to a 1-hour value.

    Response: Section 3.2 *Acute Exposure Duration Adjustments* has been revised to address this issue.

63. Comment Page 21: Panel members suggested adding the C x T discussion to the body of the report rather than having it in an appendix. Adding a figure to demonstrate the relationships will help readers understand the approach. In addition, it was suggested that the dosimetry and duration adjustment issues discussed in Chapter 3 are not specific to developing acute ESLs and should be moved to the "common procedures" chapter.

    Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

5.6.2 Dosimetry for Particles

64. Comment Page 22: Panel members found the section on particle dosimetry confusing . . .
    Response: In response to panel member comments, the Acute and Chronic sections have been combined into one section and placed in Chapter 2 *Common Procedures* . . . These sections have been rewritten to clarify the purpose of the section and to incorporate the suggestions of the panel members. The references that are mentioned by the panel members have been reviewed and incorporated into the ESL Guidelines. Specific responses to panel member comments will not be made, since the comments were more in a discussion form and technical in nature.

65. Comment Page 22: One panel member noted that there are two reasons for conducting particle dosimetry - to conduct an interspecies adjustment of dose or to define the relationship of experimental to ambient exposure.
    Response: Section *G. Issues Relating to Particulate Matter Size* was written to define the relationship of experimental particulate matter size to ambient exposure particulate matter size.

Refer to the revised Section 2.9.3 *Procedures to Evaluate Differences between Experimental and Ambient PM Exposures*. Section 2.9.2 *Default Dosimetry Adjustments for Particulate Matter* describes how to conduct an interspecies adjustment of dose for PM.

66. Comment Page 23: Panel members noted that dosimetry from RfC methods can be applied to acute ESLs– in fact given the nature of some of the parameters (e.g., gas uptake to determine partition coefficients), one can argue that DAF are more appropriate for acute exposure levels. Panel members mentioned that the MPPD model is an appropriate model to use for particle dosimetric adjustment for short-term exposures in addition to chronic exposures. The document should note distinctions in dose metric for acute versus chronic considerations, however. For example, peak concentration may be more appropriate than area under the curve; deposited dose may be more appropriate than retained dose. See Jarabek (1995c) and Jarabek et al. (2005) for clarification.

    Response: Suggestions made by the panel have been incorporated in Chapter 2 of the revised ESL Guidelines.

67. Comment Page 23: One panel member noted that the particle dosimetry model recommended by TCEQ was not in the U.S. EPA's RfC methods document. However, another panel member stated that the MPPD fits the criteria described in the RfC methods for selecting a dosimetry model. This panel member noted that the TCEQ document must also define the criteria it will use to select an appropriate model. It is also important to recognize that mechanistic models, as they are developed, will supplant default models. Another panel member noted that the MPPD has been peer reviewed and published in the open literature.

    Response: We agree with the panel members who stated that mechanistic models, as they are developed, will supplant default models. If the models have been peer reviewed and published in the open literature, such as the MPPD model, then the TS will use them. Refer to Section 2.7 *Conduct Appropriate Dosimetric Modeling*.

68. Comment Page 23: Also, this panel member noted that the best approach for choosing the dose metric for particles is to choose the one that fits best with the biological effect or endpoint being addressed. For example, retained dose, in contrast to deposited dose, may be a better dose metric for chronic effect levels. Other possible dose metrics include particle number, volume, and mass. For particle dosimetry, TCEQ should look to ICRP (1994) for data on activity patterns of humans in different environmental scenarios. For gas dosimetry, it is not yet possible to replace the default ventilation rate with more appropriate data. A different reviewer explained that for gasses, exercise results in a 20-fold increased delivery of the chemical to the alveoli, but that for particles, exercise results in a decrease delivery of the chemical to the alveoli. Therefore, it is important to look at activity patterns. Another panel member noted that the MPPD model and other software may allow consideration of specific activity patterns.

    Response: An analysis of activity patterns of humans in different environmental scenarios would be appropriate in a site-specific risk assessment. ESLs are intended to be generic screening levels for the general public, therefore we cannot routinely consider activity patterns in ESLs just like they are not considered in EPA's RfCs, California EPA's RELs, or in ATSDR's MRLs. However, this will not preclude us from considering activity patterns in site-specific risk assessments. No change to the ESL Guidelines is needed.

5.6.3 Dosimetry for Gasses

69. Comment Page 23: For gasses, several panel members disagreed with the approach taken in the document for acute ESLs. One panel member recommended that the book and papers discussed for the chronic ESL (Overton and Jarabek, 1989a,b; Overton, 1990) should also be incorporated into the acute ESL methods . . .

    Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. In addition, the separate sections describing dosimetry for gases in the acute and chronic chapters have been combined and are now located in Chapter 2.

70. Comment Page 23: Another panel member noted that the most important aspect in this chapter is that the determination of the point of departure must come after dosimetric and duration adjustments to a human equivalent concentration. The dosimetric adjustment factors (DAF) are then applied to the relevant effect level (e.g., BMCL or NOAEL/LOAEL).

    Response: See response to panel comment #4.

71. Comment Page 24: One panel reviewer applauded the use of dosimetric adjustments, but suggested that 20 m^3 as a default for inhalation rate in humans is incorrect because this rate is equivalent to a person doing moderate exercise for a 24 hour period. Rather, a value of 15-17 m3/day is more typical. Another reviewer noted that U.S. EPA's Risk Assessment Guidance for Superfund recommends a value of 13-14 m^3/day for the ventilation rate. However, a different panel member noted that the 20 m^3 daily ventilation rate includes sensitive subpopulation but that a lower default may not accommodate these groups.

    Response: We agree with the panel member who noted that the 20 m^3 daily ventilation rate includes sensitive subpopulation and a lower default may not accommodate these groups. No change to the ESL Guidelines is needed.

72. Comment Page 24: One reviewer noted that the equations (Comment Page 29 of document) to adjust for temporal exposure pattern are based on Haber's law, which is not appropriate for 90% of the chemicals. Nonetheless, this type of adjustment is standard for inhalation risk assessment.

    Response: We agree with the reviewer who stated that adjustments based on Haber's law is standard for inhalation risk assessment.

5.7 Approaches for Limited Data

73. Comment Page 24: Since TCEQ is required to develop acute ESLs for all chemicals, the ESL document proposed approaches for when there are limited toxicological data available. Most panel member comments focused on structure activity relationships and route-to-route extrapolation. The panel provided comments on these approaches and concluded that when there are no data on a chemical, the best approach may be to default to a "generic" ESL, similar to a threshold of regulation, rather than develop a chemical-specific ESL with an unreasonably large amount of uncertainty.

    Response: Section 3.5 *Chemicals with Limited Toxicity Data* has been incorporated into the ESL Guidelines to provide procedures to develop short-term ESLs for chemicals with limited toxicity data.

74. Comment Page 24: One panel member noted that Figure 2 implies that there are cases where TCEQ would not set long-term ESLs. TCEQ replied that they are required to set short-term ESLs for all chemicals, but not long term ESLs. TCEQ will not develop a long-term ESL if the data are

not available to support a value. For example, TCEQ would not set a long term ESL based on only an LC_{50}.

Response: The TCEQ is required to set short-term ESLs for all chemicals. Section 3.5 *Chemicals with Limited Toxicity Data* has been incorporated into the ESL Guidelines to provide procedures to develop short-term ESLs for chemicals with limited toxicity data. The TCEQ will not develop a long-term ESL if the data are not available to support a value. Refer to Figures

75. Comments on Pages 24-24 Structure Activity Relationships

Response: Since Section 3.5 *Chemicals with Limited Toxicity Data* has been incorporated into the revised ESL Guidelines, the panel member comments on Structure Activity Relationships no longer apply. The TS will use structure activity relationships and toxicity information on chemical classes as supporting information only.

76. Comments on Page 25 Route-to-Route Extrapolation

Response: Section 2.13 *Route-to-Route Extrapolation* has been updated to incorporate the comments of the panel and also the updated approaches for route-to-route extrapolation in the suggested references. Also, refer to Section 3.5 *Chemicals with Limited Toxicity Data*.

77. Comments on Page 26 Generic ESL

Response: Suggestions made by the panel have been incorporated in Section 3.5 *Chemicals with Limited Toxicity Data*.

5.8 Uncertainty Factors

78. Comment Page 26: Overall, the panel agreed with the approach to uncertainty factors taken in the document. However, it was stated that the document should always allow default UFs to be replaced with actual data, if they are available. It seems like this is the intent in the document, but it needs to be described more completely.

Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. Refer to Section 2.11 *Apply Appropriate Uncertainty Factors For Chemicals with a Nonlinear Dose Response*.

79. Comment Page 26: In addition, the document needs to distinguish between uncertainty factors that address lack of knowledge from factors that represent known variability in parameters.

Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. Refer to Section 2.11 *Apply Appropriate Uncertainty Factors for Chemicals with a Nonlinear Dose Response*.

80. The document should acknowledge that the UF_A and UF_H factors are composed of both kinetic and dynamic subfactors.

Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. Refer to Section 2.11.1 *Interspecies and Intraspecies UFs.*

81. Comment Page 26: One panel member noted that the rationale for the use of an modifying factor in the RfC methods is described erroneously . . .

Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. Refer to Section 2.11.4 *Rationale for Not Using a Modifying Factor*.

82. Comment Pages 26-27: Another reviewer noted that the approach in the document for UF for BMC modeling is inconsistent with EPA approaches. Additionally, this section mixes the concepts of benchmark response level and severity and EPA does not recommend applying an UF when doing BMC . . .
Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. Refer to Section 2.6 *Determine the POD*.

83. Also, the document is incorrect regarding the effect of the slope of the dose response curve on the choice of uncertainty factor for LOAEL to NOAEL. The correct application is a steep slope requires a smaller UF and a shallow slope requires a larger UF.
Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

84. Comment Page 27: The panel also discussed how children should be taken into account when selecting uncertainty factors. Panel members acknowledged that it is critical to consider the response of children since they may respond differently from adults. However, panel members also felt that an additional UF for children was not necessary and that the UF_H and UF_D already adequately protect children. See Dourson et al. (2002) for support of this position.
Response: We agree with the panel members that felt that an additional UF for children was not necessary. For carcinogens that act through a mutagenic mode of action, an ADAF will be applied to account for the potential increase susceptibility of children.

85. Comment Pages 27-28: The panel then discussed the tables in Appendix H (H-1 and H-2) of the ESL document. . . .
Response: Tables H-1 and H-2 have been removed from the ESL Guidelines and replaced by a table from the RfC Methodology. Refer to Section 2.11 *Apply Appropriate Uncertainty Factors For Chemicals with a Nonlinear Dose Response*.

86. Comment Page 28: One panel member noted that the last column in Table H-2 is not consistent with TCEQ's stated application and indicated that TCEQ must select appropriate uncertainty factors based on their application and methods . . .
Response: Table H-2 has been removed and replaced by a table from the RfC Methodology. Refer to Section 2.11 *Apply Appropriate Uncertainty Factors For Chemicals with a Nonlinear Dose Response*.

87. Comment Page 28: There was some discussion about human variability for odor and irritation. One panel member asked if there was less intraspecies variability for mild effects and another replied that the comment applied mostly to irritation. Humans are not as sensitive as animals to irritation. Another panel member stated that the human variability for odor perception is very large, so it is important to look at the actual data.
Response: We agree. The ESL Guidelines acknowledges that "the reported odor threshold data differ considerably. It is not uncommon for reported odor threshold values to range over several orders of magnitude for the same chemical." The TCEQ frequently receive complaints about odor problems, so an ESL that evaluates odor potential is an important consideration for welfare. No change to the ESL Guidelines is needed.

88. Comments on Pages 28-29 concerning Cumulative Risk
Response: Comments on cumulative risk have been addressed previously.

5.11 Odor/Acute Effects

89. Comment Page 31: The panel also discussed the issue of sensitization, with one panel member noting that the document is not clear as to whether or not sensitization *per se* or exacerbation of existing asthma is the basis of acute ESLs . . .
Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines. Refer to Section 2.15 *Sensitization*.

5.12 Mixtures

90. Comment Page 31: In general, panel members felt that the approaches described for mixtures assessment were appropriate. . . . Another panel member stated that for dioxins, the TEFs only address receptor-linked toxicity and does not address other toxicities that are not Ah receptor mediated.
Response: Consistent with this comment, the executive summary of the *Assessment of the health risk of dioxins: re-evaluation of the Tolerable Dailty Intake (TDI)* (World Health Organization European Centre for Environmental and Health International Programme on Chemical Safety, 1998) states, "For the mono-ortho PCBs especially, certain endpoints such as carcinogenicity, porphoryrin accumulation, alterations in circulating thyroid hormone concentrations and neurotoxicity could arise by both Ah receptor-mediated and non-Ah receptor-mediated mechanisms. In addition, non-Ah receptor-mediated mechanisms of action of the mono-ortho PCBs may be shared by certain di-, tri-, and tetra-chloro ortho-substituted PCBs. This increases uncertainty in the use of TEFs for mono-ortho PCBs. While recognizing that these and other uncertainties exist in the use of the TEF concept for human risk assessment, pragmatically it remains the most feasible approach. Use of TCDD along as the only measure of exposure to dioxin-like PCDDs, PCDFs and PCBs severely underestimates the risk to humans form exposure to these classes of compounds. Thus the TEF approach is recommended…"

However, if adequate information on toxicities that are not Ah receptor-mediated is available, then this information will be considered in setting a ReV for the dioxin.

91. Comment Page 31: For non co-planar dioxins and PCBs, it is more appropriate to use EPA's PCB assessment.
Response: For non-planar dioxins and PCBs, if ESL development is necessary, the most current, scientifically-defensible guidance will be used to develop toxicity values.

5.13 Policy

92. Comment Page 31: Although the charge did not direct the panel to discuss policy choices made by TCEQ, the panel did offer comments on some policy issues. The panel noted that the ESL document makes a number of science policy choices, for example using a cancer risk 10^{-5} versus 10^{-6} or using a HQ of 0.1 versus 1, without offering substantive rationale as to their basis. The panel suggested that the credibility of the procedures would be greatly enhanced if such a rationale was provided. TCEQ replied that these choices were made in order to be consistent with other State programs.
Response: The guidelines have been revised to elaborate on the rationale behind this policy decision. Refer to Section 1.4 *Specific Risk Management Objectives (No Significant Risk Levels*).

5.14 General Recommendations Pages 32-33

93. Comment Page 32: One panel member noted that some of the acronyms listed in the glossary are only used once and suggested that those acronyms should not be used, but the term should be spelled out.
    Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

94. Comment Page 33: One panel member indicated that Chapter 1 is excessively prescriptive but at the same time too skeletal and improperly placed before introducing the rationale introduced for specific derivations. To aid comprehension and appreciation of the recommended approach, this panel member suggested making Chapter 1 more of an introduction of general definitions and intent but leave details until later in the text. This reviewer suggests moving the second half of this chapter to a summary about how all the information is put together in a risk characterization.
    Response: The panel member comment was not clear. These suggested changes will not be incorporated in the revised ESL Guidelines.

95. Comment Page 33: One panel member suggested that TCEQ not use roman numerals for numbering sections in document, because this numbering system was confusing.
    Response: Suggestions made by the panel have been incorporated in the revised ESL Guidelines.

96. Comment Page 33: One panel member noted that consideration of vegetation effects is one of the three main ESL estimates for short-term characterization yet the methods are summarized in two paragraphs on Comment Page 9. Therefore, this section should be expanded to encompass current scientific data on assessing plants.
    Response: The vegetation-based ESL section was modified slightly. However, current weight of evidence indicates that conservatively-derived toxicity values that protect human health almost always would also be expected to protect vegetation. There are a few exceptions to this, e.g., ethylene. The TS does not believe the NAAQS guidance provides generally applicable guidance for vegetation-based ESL development given the paucity of vegetation toxicity data for chemicals for which ESLs are developed. The TS will consider incorporation of additional guidance and data as they become available.

97. Comment Page 33: TCEQ should define a database for vegetative effects and use UF when those data are not available to inform the deliberations of the TS scientists – otherwise there will be little, if any, incentive to provide the data.
    Response: The ESL for vegetative effects is set at the threshold (i.e., the lowest concentration where adverse effects are noted in the study). Therefore, UFs won't be applied. This statement will be included in the revised ESL Guidelines. If information on vegetative effects for a chemical is not available, then a vegetative-based ESL will not be developed for the chemical.

98. Comment Page 33: Further, it is not clear why vegetation effects are not considered for chronic characterization.
    Response: A chronic vegetative ESL will be developed for a chemical if adequate information is available.

APPENDIX D
WRITTEN PEER REVIEW COMMENTS FOR ODOR AND VEGETATION

Written Review of Vegetative Effects, Chapter 1.III.B.2

General Questions

1. Comment Page D-4: The Short-Term procedure of Figure 1 is adequate for acute vegetative effects, although it does not provide useful information on how vegetative effects are to be identified.
   Response: Hazard identification of vegetative effects is explained in more detail in Section 1.6.2.3 rather than in the Figure 1 (now Figure 1-1) flow chart.

2. Comment Page D-4: The Long-Term Procedure of Figure 2 is not adequate, as there is no mention of chronic vegetative effects.
   Response: The guidance document and Figure 2 (now Figure 1-2) has been revised to accommodate the development of a chronic vegetative ESL.

3. Comment Page D-4: Nitrogen is currently impacting ecosystems in many places. From the perspective of vegetation response it should not be exempt.
   Response: ESLs are developed for all substances determined by the TS to be airborne toxicants. Substances not considered to be airborne toxicants are exempt from the ESL development. Air on earth is mostly nitrogen (78 %). As the primary component of air, nitrogen is not considered to be an airborne toxicant.

Vegetation ESLs

4. Comment Page D-4: The criteria for developing vegetation ESLs are not appropriate because they do not include methods of determining threshold concentrations or the need for evaluation of dose-response relationships.
   Response: The ESL for vegetative effects is set at the threshold, i.e., the lowest concentration where serious adverse effects in sensitive species (as described in the revised guidance document) are noted in the literature.

5. Comment Page D-4: The focus on visible injury to individual plants should be replaced with functional injury, and to relationships of plants to their communities and to the abiotic environment.
   Response: Longer-term and internal effects are likely to be more significant than short-term visible injury. Short-term effects such as flower abortion (abscission of flower buds) and failure of seed filling are critical and will be specified in the document.

6. Comment Page D-5: The experience of the USEPA with Criteria Document development and the weight of evidence (WOE) approach embodied in the USEPA Review Draft Cancer Guidelines could be applied to the ESL guidance document.
   Response: The TS recognizes the existence of sparse guidance (EPA, WHO) for the development of vegetative toxicity values. Also, TS notes that even these agencies have not yet been able to apply these methods to air toxics because of the lack of data. The TS will consider incorporating these methods when supporting data becomes available.

7. Comment Page D-5: While it is quite appropriate for this document to focus on Texas vegetation, data on non-Texas vegetation should be used to evaluate likely damage to Texas vegetation from similar chemicals, as considered under Extrapolation and Uncertainty in the current Review Draft.

A basic presumption may be explicitly incorporated that plants are inherently similar unless differences are demonstrated.
Response: TS will develop Vegetative ESLs while focusing on Texas vegetation. Even the limited data available on chemical toxicity in plants demonstrates dissimilarities among plant species.

8. Comment Page D-5: It is quite appropriate to focus on serious issues rather than minor or cosmetic issues. However, the ESL development plan must be far from explicit in what constitutes a serious issue for vegetation. Again, longer term and interactive consequences are likely to be more significant than short- term and visible injury. Plants may often grow out of visible injury to a few leaves or other organs. Other short-term effects, however, such as flower abortion or failure of seed filling should be considered critical. These need to be specified in the document.
Response: The ESL guidance document will be revised to include flower abortion (abscission of flower buds) and failure of seed filling.

9. Comment Page D-5: This document does not deal realistically with vegetation effects, even though in Figure 1 there is a provision for selecting the acute vegetative ESL as the determining ESL. It is clear to this reviewer that the vegetative ESL is highly unlikely to rise to the level of controlling the regulatory process. However, the experience of the USEPA CD development process has been that vegetative effects often occur at lower concentrations than direct human health effects.
Response: Human health, odor, and vegetative-based ESLs will be developed based on the availability of data. The lowest of these ESLs will be the short-term ESL.

10. Comment Page D-6: An issue that is only briefly considered in the Review Draft is loading of vegetative biomass with toxic materials. This can represent a secondary route of exposure (by ingestion) to humans, or a tertiary route (by ingestion of grazing animals). . . .Ecosystem aesthetic values could be impacted significantly in the absence of short term, acute, visible injury to individual plants.
Response: Because the TCAA does not give the TCEQ authority to regulate air emissions beyond the direct impacts that the air emissions have to human health or welfare, the TCEQ does not set emission limits to restrict, or perform analysis to determine the impacts emissions may have, by themselves or in combination with other contaminants or pathways, after being deposited on land or water, or incorporated into the foodchain.

Written Review of Odor-Based ESLs, Chapter 1.III.B.1

1. Comment Page D-8: The data compilations that the staff relies upon are quite dated. . . .
Response: A statement has been added to the Odor-Based ESL section to clarify that any updated and/or better study will definitely be considered when deriving an odor-based ESL. The ESL Guidelines never suggests that the compilations would exclude studies performed beyond the time of the compilation.

2. Comment Page D-8: Compilations of odor thresholds have been in use for about three decades. The striking variability in values obtained from study to study has led to efforts to clean up the compilations. . . . . A book of standardized thresholds came out after the AIHA compilation (Devos et al., 1990). To a large degree, the compilation of Devos et al. relied upon the same studies as the AIHA compilation. Devos et al. did not disqualify data, they “corrected” them. One can ask how the two compilations compare. . . .
Response: We agree. We will incorporate the data compiled by Devos et al (1990) as well as the testing data gathered in Japan (Nagata, 2003) into the compilations. We will set our odor-based ESL at the lowest reported threshold using studies assessed on the same criteria established by AIHA and USEPA.

3. Comment Page D-10: These data lead me to believe that the EPA/AIHA set is systematically overestimates threshold concentrations and has many values that are incorrect by substantial factors. In light of these new results, I certainly question the use of the EPA/AIHA values at all and believe that new data gathering is probably the only way to fix the problem. Before that can be done, however, some effort to come up with better results from the literature might fill the gap.
   Response: A statement has been added to the Odor-Based ESL section to clarify that any updated and/or better study will definitely be considered when deriving an odor-based ESL. We will incorporate the data compiled by Devos et al (1990) as well as the testing data gathered in Japan (Nagata, 2003) into the compilations. We will set our odor-based ESL at the lowest reported threshold using studies assessed on the same criteria established by AIHA and USEPA.

4. Comment Page D-10: The answers to questions 3-6 are intertwined. The AIHA compilation implies that a 50% threshold is the concentration that half the people in a sample could smell and half could not. Most threshold studies have not been done this way. The value they give normally indicates a concentration that the average person can smell half time. The protective effect of that level depends upon variation within and between people. Very few investigators have reported this variation, but some modern studies have begun to collect the relevant data. Laws about odor pollution often specify that odors 2-7-fold above threshold, depending upon the regulation in a particular place, constitute nuisances, so a regulation that chooses the threshold would seem adequately stringent, if the threshold were correct.
   Response: The odor-based section in the ESL Guidelines already acknowledges the difficulty in determining thresholds based on odor potential and variation of odor perception. Since the ESLs are set to serve as guideline concentrations, it is our intent to set at levels well below the reported threshold concentrations that can cause adverse effects including odor nuisance. Therefore, we intend to set the odor-ESLs at 50% detection threshold concentration, if possible. No change in the ESL Guidelines is needed.

APPENDIX E
WRITTEN OBSERVER COMMENTS

Dr. Neil Carman (on behalf of several organizations)
Sierra Club
Lone Star Chapter

1. Comment Page E-4: TCEQ needs a toxicology review process with public accountability and transparency such as developing a full online database of toxicological information and permit reviews when ESLs are analyzed. . . One way to improve transparency and accountability is for the toxicology information to be made available in an online database that TCEQ applies in permit reviews.
   Response: Sections 1.9 *ESL Development Support Document (DSD)* and 1.11 *Public Comment and Peer-Review* discuss the processes that will be used for public comment from interested parties, public accountability, and transparency and states that the ESL Development Support Document will be available online.

2. Comment Page E-5: Need for improved documentation of the ESL Toxicological derivation process. The Effects Screening Levels (ESLs) need a system of clear and sound documentation of the derivation process that can be made available for review by stakeholders and the public interested in reviewing the supporting documentation. . . . Without a documented scientific basis for how the ESLs have been derived, the TCEQ's accountability to the public is reduced and lack of trust in the questionable ESLs becomes apparent.
   Response: The purpose of the ESL Guidelines is to document the ESL toxicological derivation process. In addition, Sections 1.9 *ESL Development Support Document (DSD)* and 1.11 *Public Comment and Peer-Review* discusses the processes that will be used for public comment from interested parties, public accountability, and transparency and states that the ESL Development Support Document will be available online.

3. Comment Page E-5: Need for improved documentation of the ESL Toxicological review process. . . Notzon also identified that the ESL "guideline" review process itself was lacking in accountability and may be excessively flexible in not following a logical guidance process.
   Response: A lay person pamphlet will be prepared to help the public understand how ESLs are developed. It will not be included in the ESL Guidelines. In addition, a lay person presentation on the permitting process, how air monitoring is conducted, and how ESLs, ReVs, and URFs are used will be prepared and posted on the TCEQ Toxicology Section website.

   At the present time, the health effects evaluation procedure is outlined in the TCEQ guidance document “Modeling and Effects Review Applicability: How to Determine the Scope of Modeling and Effects Review for Air Permits” (TCEQ, RG-324). Health effects evaluations are conducted when the Toxicology Section receives a Request for Comments (RFC) from the New Source Review Permit Engineer which lists the constituents expected to be emitted from the proposed facility. We consider the predicted short-term (one-hour average) and long-term (annual average) ground level concentrations (GLCs) as developed by computerized air dispersion modeling for each constituent. After the health effects evaluation has been completed, the toxicologist sends a memorandum, part of the public record, to the permit engineer providing information on the health effects evaluation.

   In addition, individuals may contact Office of Public Assistance or other agency staff by calling a toll-free phone number, 1-800-687-4040, to obtain information about agency permits and the

permitting process, or to express their concerns about either of these topics. The TCEQ also provides assistance to the public through the Environmental Equity Program and refers specific questions about the legal aspects of dealing with the commission, its hearings, and its rules, to the Office of the Public Interest Counsel.

4. Comment Page E-6: Professional criticism of TCEQ's safety factors in ESL derivation, particularly carcinogenic substances such as benzene, 1,3-butadiene, dioxin, formaldehyde, acetaldehyde, carbon tetrachloride, methylene chloride, vinyl chloride, chromium VI, chloroform, tetrachloroethylene, polycyclic aromatic hydrocarbons, etc. . . .There are no absolute safe levels of exposure to carcinogens. As evident, the application of rigid safety factors, especially without an empirical basis, is a flawed concept with unknown consequences to public health."
Response: Chapter 1 of the ESL Guidelines states that ESLs derived for carcinogens with a linear dose response are assumed not to have a threshold but are set at concentrations that correspond to a No Significant Risk Level. Refer to Section 1.4 *Specific Risk Management Objectives (No Significant Risk Levels).* ESL Guidelines references the *Guidelines for Carcinogen Risk Assessment*, hereafter referred to as the 2005 Cancer Guidelines (USEPA 2005a; Federal Register 2005a) and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (USEPA 2005b; Federal Register 2005b), as the main source of information to derive carcinogenic URFs and ReVs, which are used to determine long-term ESLs for carcinogenic chemicals. However, if it is determined based on a mode of action analysis that a carcinogen has a nonlinear dose response (i.e., a threshold), then it is acceptable toxicological practice to apply uncertainty factors to derive a long-term health-protective air concentration for a carcinogen.

Comments of Texas Chemical Council (TCC) Regarding
Development of Effects Screening Levels, Reference Values, and Unit Risk Factors

1. Comment Page E-11: TCC Supports Explicit Recognition That Exposures Above an ESL Are Not Necessarily Indicative of Adverse Health Impacts. . . . TCC believes that an objective and transparent presentation of ESLs, with explicit recognition that true risks are likely to be below estimated upper bound risks, would help prevent such misunderstanding and misapplication of ESLs. This might be more efficiently and effectively accomplished by including a statement at the beginning of each ESL assessment document that defines the ESL explicitly as a level of a chemical in air that, even if exceeded, would not necessarily be expected to result in adverse human health effects.
   Response: The ESL Guidelines already states "If predicted airborne levels of a contaminant exceed the ESL, adverse health or welfare effects would not necessarily be expected to result, but rather triggers a more in-depth review, . . ." and "Since UFs are incorporated to address data gaps and other uncertainties, exceeding the ReV does not automatically indicate an adverse health impact." No change to the ESL Guidelines is needed. However, the definitions of the ESL and the ReV will be included in the Derivation Support Document.

2. Comment Page E-12: TCC Does Not Support Use of a Target Hazard Quotient of 0.1. The Review Draft indicates that the TCEQ Toxicology Section (TS) will use a target hazard quotient (HQ) of 0.1 to calculate screening levels for noncarcinogenic constituents (p. 6), but does not explain why the TS will use a HQ other than the more typical value of 1.0. TCC believes the target HQ for noncarcinogenic effects should not be less than 1.0. . .
   Response: The ESL Guidelines have been revised to include Section 1.3 *General Risk Management Objectives* and Section 1.4 *Specific Risk Management Objectives (No Significant Risk Levels*.

3. Comment Page E-13: TCC Would Not Support Use of a Risk Management Goal for Carcinogenic Effects More Restrictive Than 1×10^{-5}
   Response: The risk management goal for carcinogenic effects is 1×10^{-5}, a no significant risk level. The revised ESL Guidelines have been revised to include Section 1.3 *General Risk Management Objectives* and Section 1.4 *Specific Risk Management Objectives (No Significant Risk Levels*.

4. Comment Page E-13: TCC Supports Peer Review and Public Comment on Proposed ESL Values . . . However, TCC believes the process may not be sufficient in all cases. In particular, the specified 30-day comment period may be insufficient for some data rich substances, particularly where difficult risk assessment choices are made. . .
   Response: The ESL Guidelines has been revised to include the following statement: "For data-rich substances, additional time may be allowed to interested parties to submit information and/or comments on the proposed DSD."

5. Comment Page E-13: Also, in many cases, an independent, external peer review may be appropriate, and where that occurs, TCC believes TCEQ should invite public comment on the peer review report and make those comments available to the peer reviewers.
   Response: Refer to Section 1.11 *Public Comment and Peer-Review*.

6. Comment Page E-13: TCC Supports the Use of Data over Default Assumptions
   Response: We agree. This is stated in the revised ESL Guidelines.

7. Comment Page E-14: Assignment of Confidence Levels to ESLs Should Not Imply That Values Might Be Under-Protective. The Review Draft describes a process for assigning confidence levels to the key study used to derive an ESL, to the database as a whole, and to the final ESL. (See p. 20) The process resembles the process used by EPA for assigning confidence levels to inhalation reference concentrations. TCC is concerned that this process could give stakeholders an unduly negative impression of ESL values by implying that the values are equally likely to be too high (under-protective) or too low (overly protective). . . .
   Response: The TS acknowledges that a confidence level assigned to an ESL is likely to be misunderstood to describe level of confidence in the health protectiveness of that ESL rather than the actual description of confidence in the basis (key study and supporting studies) of that ESL. Confidence levels will be assigned to the key study and the database, but not directly to the ESL. Uncertainty factors are applied as needed and appropriate to adjust for deficiencies in knowledge of a chemical's toxicity, resulting in ESLs whose health protectiveness is highly certain even though the confidence levels assigned to chemical databases may vary. Refer to Section 2.14 *Assignment of Confidence Levels*.

8. Comment Page E-14: Application of a 10-Fold Uncertainty Factor to a BMCL Level is not Generally Accepted
   Response: Section 2.6 *Determine the POD* of the ESL Guidelines has been revised based on panel member and TCC comments.

9. Comment Page E-15: Selection of Uncertainty Factors For Acute ESLs Should Be Made Carefully . . . Beyond the mention above of the need to replace default uncertainty factors with alternative factors that are based on data, there is a need to better explain uncertainty factors for acute ESLs**. . . . . .** For example, the Review Draft (p. 27) describes UFs for converting lethal effects levels to ESLs. In that section, use of a UF of more than 10,000 is discussed. . . .
   Response: The section of the ESL Guidelines discussing uncertainty factors has been revised based on panel member and TCC comments. In addition, Section 3.5 *Chemicals with Limited Toxicity Data* has been incorporated into the ESL Guidelines to provide procedures to develop short-term ESLs for chemicals with limited toxicity data.

10. Comment Page E-15: The TCC suggests TCEQ instead consider adopting some of the procedures and factors for deriving Acute Exposure Guideline Levels (AEGLs) as referenced in the National Research Council's AEGL Standing Operating Procedures (NRC, 2001). . . .
    Response: Each reference value system has a specific reason for existence. The purpose of AEGLS are emergency response values designed to be used in rare, accidental releases. AEGLS define a threshold effect level while maintaining public safety. The purpose of ESLs are screening levels, are set to protect sensitive subpopulations, and are meant to protect the general population to intermittent exposure. The ESL Guidelines does reference and use many of the procedures recommended in the AEGL Standing Operating Procedures (NRC, 2001). No change to the ESL Guidelines is needed.

11. Comment Page E-16: When Estimating NOAELs from LOAELs, TCEQ Typically Should Apply a Factor of 3X. TCC suggests replacing the default factor of 10X for estimating NOAELs from LOAELs with a 3X factor. . . .
    Response: It was always the intent of the ESL Guidelines to apply a LOAEL to NOAEL UF of up to 10, rather than automatically applying a full value of 10, based on the chemical's mode of action. The ESL Guidelines states "Typically, a default UF of 10 is used to adjust the LOAEL to a NOAEL. However, an UF less than 10 may be justified."

12. Comment E-16: As shown in the table below, the central ratio is typically close to a value of 3.

Response: Typically, the 95th percentile is used, rather than the central ratio, to establish health-protective UFs. For instance, Alexeeff et al. (2002) analyzed 215 data sets from acute inhalation studies demonstrating the mild effects of 36 hazardous air pollutants in order to evaluate the distribution of the LOAEL to NOAEL ratios. This study showed that for mild adverse effects, LOAEL to NOAEL UFs of 2.0, 5.0, 6.3, and 10.0 corresponded to 50th, 90th, 95th, and 99th percentiles, respectively. Based on the Alexeeff et al. (2002) study and guidance in OEHHA (1999), the TS uses a LOAEL to NOAEL UF of 6.3, which is the 95th percentile, if the acute health effect is judged to be mild. TS staff are aware that each individual UF is generally conservative, and multiplying several areas of uncertainty (four or five values of 10) likely yields unrealistically conservative ReVs (USEPA 1994). Refer to Section 2.12 *Evaluating the Reasonableness of all Risk Assessment Decisions*.

13. Comment Page E-18: EPA IRIS Values Should Be Used With Caution
    Response: We agree that it would be more appropriate for TCEQ to use IRIS as a source of information – a starting place for analysis – rather than as a source of finished values. Refer to Section 4.1 *Published Toxicity Factors.*

14. Comment Page E-19: TCEQ Should Not Rely on Toxicity Values Developed By Other States
    Response: We agree that it would be more appropriate for TCEQ to use values or documentation developed by other states as a source of information – a starting place for analysis – rather than as a source of finished values. Refer to Sections 3.1 *Published Toxicity Factors or Guideline Levels* and 4.1 *Published Toxicity Factors.*

15. Comment Page E-19: HEAST Values Should Not Be Used
    Response: HEAST values and the studies they were based on will be used as a source of information – a starting place for analysis – rather than as a source of finished values. Refer to Section 4.1 *Published Toxicity Factors.*

16. Comment Page E-19: Adjustments for Discontinuous Exposure Should Be Determined To Be Scientifically Appropriate In Each Case Where They Are Made, And An UF Of 10 Should Not Automatically Be Applied In Every Case Where a Chronic Study Is Lacking
    Response: Section 4.2 *Duration Adjustments* dealing with adjustments for discontinuous exposure to continuous exposure has been revised to indicate that TS staff will consider in each case whether a duration adjustment is scientifically appropriate based on the mode of action of the chemical.

17. Comment Page E-20: Similarly, TCC believes TCEQ should not automatically add a UF of 10 whenever a chronic study has not been conducted (as has been done in many cases in IRIS). Such a practice creates an incentive for the conduct of chronic studies even where such testing is not scientifically justified (such as where the National Toxicology Program or EPA under the Toxic Substances Control Act has determined that chronic toxicity testing is not warranted). . . .
    Response: It was always the intent of the ESL Guidelines to apply an UF of up to 10, rather than automatically applying a full value of 10, based on the chemical's mode of action. However, Section 4.4.2 *Subchronic to Chronic UF* has been revised to indicate that TS staff will consider, in each case, whether a UF is scientifically appropriate based on the mode of action of the chemical.

18. Comment Page E-20: TCC Believes That When Human Data Are Used, the Point of Departure Typically Should Be Based on the MLE, Not the UCL. . . .However, historically, EPA has used the MLE (maximum likelihood estimate) when deriving unit risk factors (URFs) from human data, and the new cancer risk assessment guidelines do not offer any scientific rationale for changing that policy, nor is it even clear from the new cancer risk assessment guidelines that this issue was

addressed during the external peer review of the new cancer risk assessment guidelines . . .. TCC believes that use of the MLE is scientifically appropriate in most cases for URFs derived from human data, and that the upper confidence limit (UCL) should be used with human data only where substance-specific justification is presented. . . .
Response: Of the unit risk factors developed by IRIS based on human data, some were derived using the MLE as the point of departure (i.e., benzene, chromium VI, and arsenic) whereas the majority have used the UCL (e.g., 1,3 butadiene, nickel refinery dust (and nickel subsulfide), coke oven emissions, benzidine, acrylonitrile, cadmium, and beryllium). The 2005 Cancer Guidelines references the SAB who stated "it may be appropriate to emphasize lower statistical bounds in screening analyses and in activities designed to develop an appropriate human exposure value, since such activities require accounting for various types of uncertainties and a lower bound on the central estimate is a scientifically-based approach accounting for the uncertainty in the true value of the ED10 [or central estimate].” When TS staff develop a URF for a carcinogen based on human data, we will consider the various types of uncertainties of the human study (i.e., substance-specific justifications) to determine whether to use the central estimate (i.e., MLE) or the UCL as the point of departure. Refer to Section 4.5.3.1 *Derivation of a POD Based on Observed Data*.

19. Comment Page E-21: TCEQ Should Be Cautious in Its Use of an Additional Factor to Account for Susceptibility Due to Early-Life Exposure to Carcinogens. . .
Response: We agree. An additional factor to account for susceptibility due to early-life exposure will only be applied to carcinogens that have been identified by the scientific community in peer-reviewed literature as acting through a mutagenic mode of action. Refer to Section 4.5.4 *Evaluating Susceptibility from Early-Life Exposure to Carcinogens.*

20. Comment Page E-21: TCEQ Should Make Sure That Its Risk Assessment Choices Are Scientifically Reasonable As A Whole. . .
Response: We agree. Section 2.12 *Evaluating the Reasonableness of all Risk Assessment Decisions* has been added to Chapter 2. This section discusses the need for TS staff to consider whether the aggregate impact of all risk assessment decisions is not overly conservative.