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 (TCEQ)

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Peer Reviewed organized by
Toxicology Excellence for Risk Assessment (*TERA*)
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Executive Summary

This Peer Review meeting of the Texas Commission on Environmental Quality (TCEQ) Technical Guidance Document was organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and consultation meetings for private and public sponsors since 1996 (see http://www.tera.org/peer/ for information about the program and reports from meetings). The Toxicology Section (TS) of TCEQ has developed a methodology for the derivation of Effects Screening Levels (ESLs), Reference Values (ReVs), and Unit Risk factors (URFs) (hereafter referred to as the ESL Methodology). The TS closely follows procedures provided in established guidance documents, therefore, a detailed discussion of well-established procedures is not included in the ESL Methodology document. Instead, a brief summary of these procedures is described with the appropriate guidance document references included. However, if the guidance procedure was not clearly defined, contained different or multiple recommendations, or the TS used procedures other than those recommended by established guidance, then a discussion was included to clarify the selected approaches.

The ESL Methodology Peer Review Panel consists of eight members. In addition, Dr. Michael Dourson of *TERA* served as the panel facilitator. The members of the panel are leading experts in acute and chronic inhalation toxicology, methods for setting ambient air exposure guidelines, cancer and noncancer risk assessment methods, and air toxics issues. Collectively, this panel has many publications and presentations, as well as service on numerous advisory panels on topics related to this peer review. *TERA* developed a "charge" document that identified the scientific issues to be discussed by the panel. The panel received a copy of the submission, the charge, and key references approximately a month prior to the meeting to ensure adequate time to carefully review the document. The meeting was organized to make the best use of the time available to hear the opinions of the experts on the charge questions. The meeting began with panel introductions and disclosure of any conflict of interest or bias issues. The authors of the document made a short presentation to highlight the salient points and issues and to give the panel the opportunity to ask clarifying questions. In addition, two observers presented short statements to the panel. The discussion then addressed the sponsor's ESL Methodology document.

Over the course of the meeting, the panel discussed each chapter of the document according to the charge questions**.** However, during the discussions, it became clear that most of the issues raised by the panel members were applicable to all aspects of the document, not just a single chapter or charge question. Therefore, this report presents the panel discussion organized by technical issue, rather than by chapter or charge question. The panel made some general recommendations for improving the clarity of the document and then discussed the following issues: appropriate data sources, hierarchy of approaches to risk assessment, determining critical effect and appropriate point-of-departure, cancer risk assessment, appropriate uses of dosimetry, appropriate approaches for dealing with limited data, choice of uncertainty factors, approaches for assessing cumulative risk, chemicals exempt from ESL development, and odor and other acute effects.

Overall, the panel concluded that the document incorporates the most current and relevant federal and state guidance. The panel suggested that the criteria for selecting data sources for chemical-

specific values should include peer review and public involvement. 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 assessments 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.

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.

The panel made several suggestions regarding the selection of the critical effect and point of departure, including choosing the appropriate dose metric and conduct dosimetric modeling **before** selecting critical effect and POD, and selecting the point of departure using an approach that fits data using a mathematical model, such as benchmark modeling.

The panel suggested that treatment of Haber's Law and duration adjustments is outdated and several new publications should be incorporated to bring it up to date. Specifically, 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. The panel suggested 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 that chronic exposures.

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.

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.

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. The document should develop HQs for the noncancer properties of carcinogens and consider them in the cumulative risk assessment.

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. 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.

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. 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.

1. Participants

Sponsor

Michael Honeycutt
Toxicology Section
Texas Commission on Environmental Quality

Meeting Facilitator

Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA*)

Peer Review Panel Members*

Craig Beskid
Mickey Leland National Urban Air Toxics Research Center

Gary Foureman[1]
U.S. Environmental Protection Agency
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Rogene Henderson
Lovelace Respiratory Research Institute

Annie Jarabek
U.S. Environmental Protection Agency
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David Kelly
DuPont Company
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Fred Miller
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Maria Morandi
University of Texas School of Public Health

[1]Dr Foureman was selected as a panel member, but was unable to participate in the review due to a personal emergency.

Deidre Murphy
U.S. Environmental Protection Agency
Office of Air Quality, Planning and Standards
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Observers and Other Attendees

A list of observers and other attendees is found in Appendix A.

2. Background

This Peer Review meeting of the Texas Commission on Environmental Quality (TCEQ) Technical Guidance Document was organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and consultation meetings for private and public sponsors since 1996 (see http://www.tera.org/peer for information about the program and reports from meetings).

The Toxicology Section (TS) of TCEQ has developed a methodology for the derivation of Effects Screening Levels (ESLs), Reference Values (ReVs), and Unit Risk factors (URFs) (hereafter referred to as the ESL Methodology). ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects, while long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects. ESLs are used in the evaluation of air permit applications as well as proposed rules and regulations (e.g., Permits By Rule). Reference values (ReVs) and Unit Risk Factors (URFs), the basis of health-based ESLs, are used in the evaluation of air monitoring data and in the development of Protective Concentration Levels for remediation sites.

The TS closely follows procedures provided in established guidance documents, therefore, a detailed discussion of well-established procedures is not included in the ESL Methodology document. Instead, a brief summary of these procedures is described with the appropriate guidance document references included. However, if the guidance procedure was not clearly defined, contained different or multiple recommendations, or the TS used procedures other than those recommended by established guidance, then a discussion was included to clarify the selected approaches.

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. The comprehensiveness of the language in the THSC resulted in the development of methodology that allowed derivation of ESLs for as many air contaminants as possible, including chemicals with limited toxicity data.

The ESL Methodology Peer Review Panel consists of eight members.1 Dr. Michael Dourson of *TERA* served as the panel facilitator. The members of the panel are leading experts in acute and chronic inhalation toxicology, methods for setting ambient air exposure guidelines, cancer and noncancer risk assessment methods, and air toxics issues. Collectively, this panel has many publications and presentations, as well as service on numerous advisory panels on topics related to this peer review.

Each panel member has disclosed information regarding potential conflicts of interest and biases related to the work product of the peer review (the ESL Methodology document) or to the sponsor of the work product (TCEQ). *TERA* evaluated these disclosures when selecting panel members. Short biographical sketches and disclosure statements for panel members are provided in Appendix B.

TERA developed a "charge" (see Appendix C) document that identified the scientific issues to be discussed by the panel. The panel received a copy of the submission, the charge, and key references approximately a month prior to the meeting to ensure adequate time to carefully review the document. The meeting was organized to make the best use of the time available to hear the opinions of the experts on the charge questions. The meeting began with panel introductions and disclosure of any conflict of interest or bias issues. The authors of the document made a short presentation to highlight the salient points and issues and to give the panel the opportunity to ask clarifying questions. The discussion then addressed the sponsor's ESL Methodology document. In addition to the panel members' discussion, an expert in the field of vegetative effects of air pollutants and in the field of odor thresholds were asked to provide written reviews of vegetative ESL and odor ESL methods, respectively. These written reviews are provided in Appendix D.

Members of the public were invited to attend the meeting and observe the panel discussions. The public also was given the opportunity to submit comments on the draft framework document for the panel's consideration. Copies of these written comments are included in Appendix E. Two individuals provided oral comments at the meeting. These comments are summarized in the text of this report.

TERA prepared this meeting report. The report summarizes the sponsors' presentations, the panel discussions, the sponsors' responses to questions, and any comments from the public. The meeting report is a summary, not a transcript. Individual opinions of the panel members are noted (although not identified by name), along with areas of agreement and disagreement. Panel members have reviewed and commented on the draft report. The sponsor was given the

[2]Nine panel members were initially selected, but Dr. Gary Foureman was unable to participate due to a personal emergency.

opportunity to review the draft report to confirm the accuracy of the sponsor presentations and comments. This report is available on the Internet at http://www.tera.org/peer/TCEQ/TCEQWelcome.htm.

3. Introductions, Conflict of Interest, and Meeting Process

The meeting opened with a welcome by Ms. Joan Strawson of *TERA*. She noted that copies of panel members' biosketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees (see Appendix B). Panel members then introduced themselves and all indicated that they had no additions or changes in their disclosure statements.

Dr. Dourson, the meeting facilitator, described how the meeting would be conducted. He explained that discussions would be based on the items found in the Charge to the Panel (located in Appendix C). He noted that all panelists would have the opportunity to state their own positions on the charge items and to ask one another clarifying questions and further discuss the issues. The facilitator indicated that where possible he would guide the panel to develop consensus positions on the charge questions; however, consensus was not necessary. The facilitator indicated that panel members were free to ask questions or discuss issues with the authors or members of the public during breaks. However, all relevant discussion was to be brought back to the meeting to ensure a hearing by all panel members. The authors and public were asked to not initiate any discussions with the panel members.

4. Presentations and Clarifying Questions

4.1 Sponsor Presentation

Dr. Michael Honeycutt, Manager, Toxicology Section, TCEQ gave the sponsor presentation (see Appendix F for the presentation slides). Dr. Honeycutt opened his presentation with a description of the air permit review process in Texas in order to give the panel a background of how ESLs are used. The Texas Clean Air Act requires all emissions from all sources to be permitted. Even "grandfathered facilities" must obtain an air authorization by the year 2008 or cease operations. There are four different levels of permits that vary in complexity. The New Source permit is the most complex and involves a two-part review: the Best Available Control Technology review and the Health Effects review. The TS employs a screening procedure to determine which permit applications must undergo the health effects review. The health effects review is based on the air concentrations predicted by air dispersion modeling. TS uses USEPA-approved air dispersion models (e.g. the Industrial Source Complex Long Term (ISCLT) model) which predict worst-case, off-site ground level concentrations of chemicals based on maximum allowable stack and/or fugitive emission rates.

Dr. Honeycutt also briefly described TCEQ's ambient air monitoring program. The State uses both mobile monitors and fixed site monitors. Mobile monitors gather instantaneous samples and 1 to 4 hour samples for estimating short-term air concentrations. Fixed site monitors collect 24-hour samples and also continuous samples analyzed by gas chromatograph for estimating short-

term air concentrations and annual average concentrations. The air monitoring results are compared to Reference Values (ReVs) and Unit Risk Factors (URFs), the development of which is described in the ESL methodology document under review. Dr. Honeycutt also noted that ReVs and URFs are used for soil remediation clean up values based on exposure pathways of volatilization of organics or release of particles from soil.

Dr. Honeycutt then summarized the ESL methodology. ESLs are chemical-specific values set to protect human health and welfare. TCEQ develops both short-term ESLs, which protect from a 1-hour exposure, and long-term ESLs, which protect from a chronic exposure. Beginning in 2003, TCEQ developed a method for ESLs which incorporates current risk assessment approaches and uses existing guidance. The short-term ESLs are either health-based, or based on odor or vegetative effects. They are intended to be similar to California's acute Reference Exposure Levels (RELs) and draw from the REL methodology. In addition, TCEQ also consulted U.S. EPA's Acute Reference Exposure (ARE) and RfC methods, as well as the Acute Exposure Guideline Levels (AEGL) methods. The long-term ESLs are health based, and draw primarily from U.S. EPA cancer and noncancer guidance as well as from California's REL methodology.

4.2 Clarifying Questions from the Panel

Panel members asked questions about the air permitting process in Texas, the use of air monitoring data, and the ESL methods.

Panel members asked whether air permits are required for all chemicals ever created, including tobacco smoke. TCEQ replied that ESLs are required for all chemicals that are subject to air permits. Air permits only consider ambient air. However, tobacco smoke is regulated by the state health department. One reviewer wanted to know when facilities need to get new permits. TCEQ replied that permits are good for 10-15 years, but facilities must update their permits when they have a change in process. In response, a reviewer asked how are the emissions from established facilities regulated if permits are required for new or modified facilities. TCEQ indicated that, originally, the Texas Clean Air Act allowed for facilities that were already in existence to be grandfathered in, but that provision has now expired. Currently, all facilities must be permitted, and facilities become regulated as they apply new permits or modify existing permits.

One panel member asked how air monitoring data are considered in the permitting process. TCEQ replied that areas where either fixed site or mobile monitoring has detected concentrations of chemicals that approach a level of concern are placed on the agency's Air Pollutant Watch List. This triggers more detailed air permit reviews, generally resulting in either no net increases or decreases in emissions of the pollutant of concern. Panel members then asked if the evaluation of air monitoring data takes into consideration the location of the monitors or recognizes that the air concentrations of chemicals are dependent, in part, on whether the monitors are closer together or further apart. In addition, does the evaluation take into consideration that monitors are located differently in different parts of the state? TCEQ replied that air monitoring data are used to evaluate whether the emissions of the company being permitted would affect existing air levels in its location. Therefore, models are used to predict the air concentrations at the locations of the monitors in that area.

Another panel member asked how the models handle fugitive emissions and how well the models have been evaluated. TCEQ replied that, if there are good data, the models predict fugitive emissions well. However, the data tends to be better for point sources than nonpoint sources. The models have been well evaluated; where modeled concentrations are compared to measured concentrations, the models usually overestimate the air concentrations. In response, one reviewer asked how much to the models over predict air concentrations. TCEQ indicated that, generally, the models over predict by up to an order of magnitude, but it varies by chemical. For example, some organics that are present in vehicle emissions, such as benzene or butadiene, have modeled and measured air concentrations that are closer than other chemicals. Another reviewer asked whether TCEQ accounts for atmospheric transformation of chemicals in using air models for permitting. TCEQ replied that it does not consider atmospheric transformation of compounds in the permitting process, but it does permit for precursor chemicals.

Another panel member noted that the document indicates that ESLs are developed to protect welfare, yet welfare is not defined. TCEQ replied that odor and vegetative effects are considered welfare and that it has also considered corrosion in the past. Finally, professional judgment contributes to conclusions about welfare. Panel members noted that the U.S. EPA NAAQS include ecological effects and that ozone, for example, has ecological effects down to background levels. One panel member asked whether the ESL methodology allows TCEQ to remove a 10-fold uncertainty factor in the ESL derivation to account for the air modeling over prediction of air concentrations. TCEQ replied that it does not adjust the ESLs. Since modeling results are used for permitting, not for regulating ambient air, the ESLs provide a good screening value.

A reviewer asked who the target audience is for the TCEQ document. TCEQ replied that the primary target audience is TCEQ staff, and its purpose is to be a guidance document for developing ESLs in house. 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. 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.

One panel member asked about the status of the existing ESLs developed using the old methods and how many have been revised. In addition, this panel member wanted to know if TCEQ had compared the new and old ESLs for specific chemicals. TCEQ replied that none of the existing ESLs will be revised until the methodology has been finalized. Therefore, no such comparison has been done. 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.

4.3 Observer Presentation

Two observers chose to make oral comments to the panel. Dr. Stuart Cagen of Shell Chemical Company spoke on behalf of the Texas Chemical Council. Dr. Cagen’s comments highlighted three points raised in their written comments, which were submitted to the panel prior to the meeting (see Appendix E). First, Dr. Cagen expressed appreciation for the explicit recognition of

the need to protect the general public. However, Dr. Cagen commented that TCEQ should explicitly state that if exposures exceed the ReVs, adverse effects would not necessarily be expected to result. While the document notes this for ReVs, it should make similar statements about the URFs for carcinogens. Screening values are often misunderstood by the public and they may not understand that even for carcinogens, the actual or true health risks may be lower, and could be much lower than the nominal value given as the ESL

Second, while Dr. Cagen noted that the ESL development process includes a number of positive features such as a public comment process, he noted that a 30-day comment period may be insufficient for some data rich substances particularly where derivation of ESLs is complex. In addition, external peer review may be helpful for some ESLs, and the results of the peer review should be made public.

Finally, Dr. Cagen commented that the ESL process should include a step at the end of each value derivation to assess the reasonableness of the end result. He noted that too many conservative assumptions may collectively lead to derivation of a value that is scientifically unreasonable as a whole. Therefore, it is important to make sure that the aggregate result is scientifically appropriate, consistent with underlying data, and scientifically reasonable.

Following Dr. Cagen's presentation, the panel asked him some clarifying questions. One panel member asked how the observer would deal with the over conservativeness, or large levels of uncertainty, without eliminating the purpose for having an ESL. The observer suggested that the ESL documents could more clearly state the degree of uncertainty and perhaps communicate the concept of uncertainty better by not presenting the ESL as a bright line with a high degree of scientific certainty. Another reviewer noted that the normal function of the way these risk assessment documents is done includes these considerations in the risk characterization section, which should specifically indicate when the data are uncertain. This reviewer understood that the intent of the TCEQ process was to come up with a usable ESL value. If there is a large uncertainty, the resulting document needs to be structured in ways that encourage interested parties to obtain more and/or better data. This panel member thought TCEQ should provide an incentive for regulated parties to fill in data gaps and asked whether TCEQ has a policy or history of working with parties to improve its database. TCEQ replied that it happens but not frequently, but they do want to encourage this.

The second observer to address the panel was Mr. Evan Johnson of the group Public Citizen. Mr. Johnson's comments highlighted points raised in their written comments, submitted to the panel prior to the meeting (see Appendix E). Mr. Johnson indicated that he was there representing the citizens of Texas who have been victims of a gradual poisoning process from refineries and facilities. He told the panel that these people have been affected by high pollution levels and the decisions made by the panel will affect them more. Mr. Johnson particularly addressed the use of TLVs as the basis of ESLs. He indicated that TLVs should not be used for the general population; they were designed to protect for shorter exposures (work week) and for the average worker who is in good health and median age. In addition, workers are warned of risk and trained to limit exposure. Mr. Johnson indicated that TCEQ should develop a new health-based approach. In addition, he stated that TCEQ's current approach for cumulative risk is not appropriate because it

relies on standards from single exposures, not mixtures and suggested that TCEQ follow EPA guidance for cumulative risk.

Following Mr. Johnson's presentation, the panel asked him some clarifying questions. One panel member noted that the method document seems to step away from using the TLV as the basis of the ESL and asked the observer whether he had any specific comments to make on the new approaches. The observer noted that they should err on side of caution. Another panel member noted that the TLV is an upper bound value and thought it should not be used as the basis of an ESL, but it is a reasonable cross check. In addition the reviewer noted that the occupational area is rich in data. One panel member noted that the observer's written comments state that there is lack of scientific peer review; this panel member asked the observer to describe the degree of peer review desired for each chemical-specific ESL. The observer replied that he realized that TCEQ is limited, but his group supports doing as much as possible to help Texans at risk. He encouraged TCEQ to use as much solid scientific evidence as possible. While this is not always possible, if causation cannot be established, TCEQ should at least err on the side of caution in order to lower rates of cancer and other health risks.

5. Discussion

Over the course of the meeting, the panel discussed each chapter of the document according to the charge questions (see Appendix C)**.** However, during the discussions, it became clear that most of the issues raised by the panel members were applicable to all aspects of the document, not just a single chapter or charge question. Therefore, this reports presents the panel discussion organized by technical issue, rather than by chapter or charge question. The panel made some general recommendations for improving the clarity of the document and then discussed the following issues: appropriate data sources, hierarchy of approaches to risk assessment, determining critical effect and appropriate point-of-departure, cancer risk assessment, appropriate uses of dosimetry, appropriate approaches for dealing with limited data, choice of uncertainty factors, approaches for assessing cumulative risk, chemicals exempt from ESL development, and odor and other acute effects.

5.1 Data Sources

In reaching conclusions about the adequacy of the data sources used by TCEQ, the panel members considered whether the document was based on the most current and relevant guidance and whether the sources and hierarchy of sources for published acute and chronic toxicity values were complete and appropriate. Generally, the panel members recognized that finding and evaluating the available data on a chemical is a sound scientific approach concluded that TCEQ should place less emphasis on adopting "ready made" toxicity values. However, one panel member noted that the approach of reviewing the available "ready made" toxicity assessment in the context of the currently available information is the most practical and also suitably defensible approach for TCEQ. This issue is discussed more completely in Section 5.2, Hierarchy.

In general, the panel thought that the document was based on the most current and relevant federal and state guidance. One panel member commended TCEQ on staying current because it

is often difficult to keep contemporary with the state of the science and policy at U.S. EPA. 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. One panel member felt that children's health issues were not well addressed, while another added that the database uncertainty factor addressed children's health issues. 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.

Several panel members found the document to be unnecessarily focused on U.S. guidance. These reviewers noted that there are very good guidance documents available from the OECD, IARC and the WHO. Given ready access via the web and the fact that we are in the age of a global marketplace, it makes sense to utilize the information and data that have been made available by industry partners and others to support these other regulatory efforts. The Air Quality Guidelines available from the WHO (1987) are especially useful.

For acute ESLs, panel members concluded that, overall, the list of sources seemed complete and the proposed hierarchy was appropriate. Except, one reviewer noted that the Immediately Dangerous to Life and Health (IDLH) values were less relevant than other proposed values and suggested moving these to the bottom of the list. Another reviewer recommended the Short-term Exposure Limit (STEL) and ceiling limits as far more relevant than the IDLH. Several panel members noted that the Emergency Response Planning Guidelines (ERPGs) were not developed to protect exposed populations against repeated exposures. Short-term Public Exposure Guidance Levels (SPEGLs) were developed as community protection values, but there are very few of them; they are at least 20 years old and are generally not well considered or available to the general public. Another panel member noted that the department of energy has developed Temporary Emergency Exposure Limits (TEELs). However, these values do not have a public process or peer review and do not carry the same weight as the AEGLs and ERPGs. Other panel members noted that the IDLH values divided by 10 have been used in emergency planning programs as a level of concern, and that this approach would be preferable to TEELs. Another panel member noted that although the occupational values are a good source of information, the actual values are not appropriate for community protection. For example, occupational values may not based on effects of concern to the general population, such as developmental toxicity. In these situations, an occupational value will not be protective for the general population. In addition, the emergency planning values only consider a single exposure situation, not continuous, short-term exposures. Even AEGLs, which are more rigorously derived values, assume a single event, not continuous exposure.

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. TCEQ replied that they are mandated to develop acute ESLs for all chemicals, and that when information is lacking for a chemical, they would rather use a longer-term study than resort to developing an ESL from a TLV

or LC_{50}. Another panel member encouraged TCEQ to make the terminology in the document consistent with standard terminology used in inhalation toxicology. This panel member noted that in standard terminology "acute" exposure is up to 1 week, "subchronic" exposure is up to 90 days, and "chronic" exposure is longer than 90 days. However, this reviewer noted that it is acceptable risk assessment practice to incorporate longer term data to develop acute risk values. However, another panel member pointed out that this practice is only acceptable when it is justified by the mode of action analysis.

For chronic ESLs, panel members thought that the sources for published values should have included more information from other groups or countries such as RIVM, Health Canada, Germany's MACs, OECD, and WHO guidelines. Data and studies from other sources such as; the public, business and trade groups, and academic research should also be consulted. Reviewers suggested that the document should list the criteria used to establish the hierarchy of published values; reviewers also suggested that peer review and public involvement should be criteria in evaluating published values. For example, ATSDR's MRLs and CalEPA values have some peer review and public comment, so these values might be placed above PPRTVs and HEAST in the hierarchy. In addition, some panel members noted that HEAST values are scientifically questionable. Although some values on HEAST have had either an external peer review or an EPA agency review, one panel member indicated that often values were placed on HEAST without revision after being criticized by review panels. Other panel members suggested that occupational data and emergency levels provide a good source of data, even though the values themselves are not appropriate as a basis of ESLs. Other panel members agreed, noting that occupational data and the documentation supporting TLVs is very robust and can be more solid than some environmental data. Another panel member suggested that the document clarify which occupational values are more useful for environmental assessment. For example, TLVs would be a better source than PELs because PELs are not strictly risk-based.

5.2 Hierarchy of Risk Assessment Approach

In evaluating the overall approach used by TCEQ to develop ESLs, the panel suggested that the document place more emphasis on evaluating available data for chemicals. In discussing this issue, the panel proposed an overall risk assessment framework that can guide TCEQ scientists in both evaluating the available data and considering whether "ready made" risk assessments are appropriate and applicable to TCEQ needs

One panel member noted that the ESL document does not address or comment on the way in which "ready made" risk assessment values will be used to develop ESLs. Another panel member agreed, noting that it was not clear if the document was describing methods TCEQ would use to derive a de novo value or adopt a "ready made" value. Nor was it clear how TCEQ would deviate from federal guidance. Another reviewer indicated that the document failed to convey the hierarchal approach that underlies the choice of dose metric and model structure used in dose-response derivation in both the 1994 RfC methods (US EPA, 1994) and 2005 EPA cancer guidelines (US EPA, 2005). These are critical issues to consider and explicitly discuss – especially as contemporary bioassays incorporate more mechanistic data.

One panel member suggested that the document should address what level of review "ready made" values will be given. The superficial nature of the description of the procedures in the document gives the impression that TCEQ is merely conducting a literature search of published risk estimates but is not critically evaluating the data, approaches or assumptions that underlie a given estimate. An explicit discussion of how the mandate and assumptions (e.g., healthy worker population or not; number of years considered a lifetime [e.g., 40 or 70]; use of dosimetry adjustment; application of safety factors (SF) or uncertainty factors (UF)) of a particular regulatory or environmental protection body influence the derivation procedures is paramount. Such a discussion for the available exposure values used to characterize risk from acute exposures can be found in Jarabek (1995a,b).

This panel member noted that without considering these types of issues, TCEQ could add significant variability to its program by adopting other programs values. TCEQ replied that it intended to evaluate existing values and review the basis for each value before adopting them. If the basis and approach are applicable for TCEQ, then they will adopt the value, but if not, they will just incorporate the data from the existing value and develop their own value. Their legislative authority indicates that they should follow U.S. EPA methods.

In the context of understanding how TCEQ would evaluate and apply "ready-made" assessments, another panel member asked how TCEQ would use an ATSDR MRL to develop an ESL, since the ATSDR approach differs from the U.S. EPA approach. TCEQ replied that they would use the ATSDR NOAEL and apply dosimetric adjustments consistent with EPA guidance; they would not use the MRL "ready made". Another panel member noted that the ESL document requires the use of the Multiple Path Particle Dosimetry (MPPD) model rather than the Regional Deposited Dose Ratio) model for particle dosimetry. While this model is clearly consistent with the RfC methodology, it represents a newer approach to dosimetry than used for most RfCs currently on IRIS. Therefore, this reviewer asked how TCEQ would evaluate an EPA RfC that was developed using the RDDR dosimetry model. TCEQ replied that they would update the EPA RfC using the MPPD model.

Panel members suggested that TCEQ consider applying the following analytical approach as the foundation of the ESL document. This analysis would apply to both evaluation of "ready made" values and data sets for which no values are available. This type of analysis would place emphasis on the availability of data, rather than the availability of a risk value. One panel member noted that the issue of peer review became more pressing as TCEQ deviated from existing assessments and created new ones.

- 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.

Panel members noted that, following this framework, the document's text needs to explain in more detail how the decisions in Figures 1 and 2 will be made. Panel members particularly noted that most of the key decisions in this framework occur between steps 1 and 2 in the flow charts in Figures 1 and 2 and the text needs to provide more discussion for all of the key decisions that occur.

5.3 Criteria/Professional Judgment

In evaluating the overall approaches taken in the ESL document, the panel members noted that in many places, the document does not describe how key decisions are made nor guide TCEQ staff on how to exercise professional judgment. Since TCEQ has indicated that the document will primarily be a manual for staff, the panel suggested that the document should more clearly describe the criteria that are used for key decisions and how to exercise professional judgment.

One panel member noted that the document should have a clear hierarchy of default assumptions and should describe the data needs to move away from defaults. In addition, it should explain the rationale for departing from stated methods and develop criteria for moving away from set procedures. In particular, panel members noted that the document often requires making the "appropriate" choice for a decision but does not define or give criteria for what is appropriate for that decision. Other panel members noted in many aspects of risk assessment, key decisions are often made using professional judgment. Since the document under review is primarily a guidance document for TCEQ staff, many panel members suggested that it describe the criteria that should be used in order to apply professional judgment for key decision points. Another panel member agreed that, as written, the document does not convey the use of professional judgment underlying the choice of dose metric and use of dosimetry. One panel member agreed that the methods should reflect the use of the best data when they are available. But when data are not available, or are only suggestive, then the methods document should reflect caution because the overall purpose is to protect public health. Therefore, the document should provide clear policy defaults and should provide criteria for when the data are good enough to move away from the defaults. Other panel members agreed, noting that this is the approach recommended in U.S. EPA's 2005 Cancer guidelines (US EPA, 2005).

One reviewer indicated that it is also critical to credibility for TCEQ to establish criteria for a minimum database for ReV derivation in the same way that EPA has defined the minimum database needed to develop a high or low confidence RfC. TCEQ should consider the objectives of the ESL values as the basis for these criteria. For example, the rationale behind the minimum database requirements for derivation of a high confidence RfC by the EPA is that the available database should contain testing-guideline (or equivalent) studies that collectively address all life stages and any potentially critical endpoint. The minimum database requirement for a low confidence RfD is one 90-day study that adequately addresses systemic toxicity and portal of entry effects. These criteria would provide a platform on which to build a framework to evaluate the available data and whether the underlying assumptions embedded in any available "ready-made" risk estimate violate the intended application by TCEQ.

For example, one panel member suggested that TCEQ evaluate its needs for acute exposure values and then define its own criteria for developing values. Only then can it evaluate the data supporting existing values. It is important to first define management objectives for ESLs, particularly acute ESLs, and then develop criteria for meeting these objectives. With the objectives and criteria in mind, TCEQ can then evaluate data and mode of action, and evaluate available values to see if they are applicable to TCEQ.

One panel member suggested that the document needed criteria for when a peer review of a chemical-specific ESL was needed. Another agreed, and also suggested that the document should describe the approach for prioritization of which chemicals to develop ESLs for first.

One panel member suggested that the document describe the criteria that were used for considering a chemical exempt from ESL development. In addition, the document should also add the criteria/data that would move a chemical off the exempt list. TCEQ replied that it mostly relied on professional judgment and intended that only chemicals that clearly belonged on the list should be there.

5.4 Critical Effects/Point of Departure

Panel members addressed several issues related to determining the critical effect and selecting the point of departure for developing inhalation risk values, including the choice of appropriate studies, the process used to select the critical effects, and selection of the appropriate point of departure.

Several panel members suggested that field studies and occupational studies should be added to the list of acceptable human studies, noting that occupational data are relied upon in the subsequent sections but are completely absent in this section. 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.

Panel members noted that the document is not consistent with EPA guidance in the process used for selecting the critical effect and critical study. EPA guidance says that the appropriate dose metric must be selected and appropriate dosimetry modeling conducted to get human equivalent concentrations before the critical effect and study can be selected. The dosimetric adjustment factors (DAF) are applied to the relevant effect level (e.g., BMCL or NOAEL/LOAEL). 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. 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.

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.

One panel member suggested that TCEQ consider using other mathematical approaches such categorical regression for selecting the POD, since the NOAEL is the weakest choice for a POD. 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.

5.5 Cancer

The panel evaluated how well the ESL document incorporated and interpreted U.S. EPA's 2005 cancer guidelines.

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. 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.

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.

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". Also, this reviewer noted that the document should recognize and indicate that the quantitative result of a cancer analysis may not be a slope factor, but rather may be some kind of "reference" value. This reviewer also noted an error in the guidelines that was carried through to

the TCEQ document. On page 38, for time-weighted averaging, should be 14/70 and 54/70 - not 13/70 and 55/70. On 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 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 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 page 38 presume a constant exposure concentration continuously over a lifetime and this presumption needs to be stated in the document. The discussion in Section C3, page 39, should be revised to accommodate that it is still possible to have a linear dose-response, even if the mode of action is not mutagenic. The appropriate approach is to evaluate the mode of action and decide the most relevant low dose extrapolation. The conclusion may be linear or nonlinear, based on the MOA evaluation. When a conclusion cannot be reached, a linear low dose extrapolation as a default is the last resort.

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).

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) 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.

5.6 Dosimetry

The panel evaluated the application of dosimetric models to the development of both acute and chronic ESLs. Comments focused on TCEQ's interpretation and application of Haber's Law as well as the dosimetry approaches taken for both particles and gasses.

5.6.1 Haber's Law

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.

One panel member noted that there are some errors in the appendix on Haber's Law. First, in the plots on page 65, the C and T axes are reversed. 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. This panel member noted that it is easy to re-enter and plot the data to re-fit the data correctly. This is a better way to use data from multiple concentration and time points. 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.

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. When extrapolating from a longer to shorter duration, one should use the concentration with no adjustment. When extrapolating from 4-week data to a shorter time, using concentration is conservative.

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. 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.

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.

5.6.2 Dosimetry for Particles

Panel members found the section on particle dosimetry confusing. It is well established that laboratory animals and humans differ in their ability to inhale particles of different sizes. Particles respirable in humans may not be respirable in animals. Once particles are inhaled, the differences in airway geometry and airflow also result in different deposition efficiencies in the various regions of the respiratory tract (e.g., extrathoracic, tracheobronchial or pulmonary) between human and experimental animals. 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. The document was not clear about whether this discussion was aimed at approaches for interspecies extrapolation or whether it was aimed at an evaluation of whether or not the experimental exposure in question such as an intermittent regimen or properties of the particles (e.g., particle diameter, distribution, hygroscopicity, solubility, speciation) was relevant to human exposures.

If the purpose is interspecies extrapolation, then one panel member suggested that the application of the dosimetry adjustment factor (DAF) or the use of a more optimal modeling approach (e.g., use of the MPPD model) would address the differences between inhalability and influences of airway architecture (geometry) and breathing pattern between species. If the purpose is to determine relevance to human exposure, then the MPPD model can be used to predict a human exposure with the specific particle size and distribution and other attributes (e.g., human ventilation activity pattern for specific ages) in question. The distributions for each case can then be compared to calculate what amount of the predicted risk from the laboratory toxicity data is relevant to the exposure of interest. References that would be especially useful in helping to clarify this section are Snipes et al. (1997) and Jarabek et al. (2005).

Panel members also discussed the role of particle size in the dosimetry of particles; particles 10 µm in diameter, as defined by PM10 are the particles that are of the most relevance for ESLs. Another panel member suggested that the document should clarify that PM10 is a 50% size-cutpoint for sampling only and does not reflect actual deposition efficiencies within the respiratory tract. Careful inspection of the distribution of an aerosol characterized as “PM10” actually includes a small fraction of particles as large as 30 um. In addition, the panel suggested that the document should also clarify what particle diameter is being used for expression of particle exposures, mass median aerodynamic diameter, count median diameter, etc. One panel member noted that if ESLs are used to evaluate monitoring data and are based on dosimetry as described, then the State should be conducting its monitoring using PM10 and PM2.5 monitors. Another reviewer noted that, while important, looking at just size distribution of particles is not enough; samples must also be evaluated for the chemicals that are bound to the particles. TCEQ replied that they use both PM10 and PM2.5 monitors and also analyze samples for the particle components. Air permits must meet the NAAQS for PM and also meet the ESL for the chemicals bound to the particles. However, the TCEQ does not adjust the ReV to account for the fact that exposure is to particle-bound chemicals. Panel members noted that this aspect should be clarified in the document. One panel member asked if the primary purpose of the document is to describe extrapolation from animal or human occupational studies in order to derive a Human Equivalent concentration? TCEQ replied yes.

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.

For dosimetry of poorly soluble particles, the equations described in Jarabek et al. (2005) eliminate the need for the equation presented on page 30, line 12. Another panel member noted that the equation will not work for hygroscopic particles or droplets. 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. 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.

5.6.3 Dosimetry for Gasses

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. These authors provide information on respiratory tract target regions and systemic uptake of gases as a function of the air:blood partition coefficient of the gas. Other panel members note that enhanced models for evaluating deposition of gasses are being developed, and the ESL methods should include provisions for using these as they become available. 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).

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 One reviewer noted that the equations (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.

5.7 Approaches for Limited Data

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 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.

Panel members indicated that the document should define what will be the minimum database for developing both high and low confidence acute and long-term ESLs (e.g., as stated before, the minimum database for a RfC is a 90-day study that adequately assesses both systemic and portal-of-entry effects) so that it can describe procedures to use when data are inadequate or when a specific type of study is missing. 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}.

5.7.1 Structure Activity Relationships

Several panel members noted that Structure Activity Relationship (SAR) is reasonable as a supporting approach, but it is not appropriate as the primary approach when there are no data. In contrast, some panel members suggested that if the data are this bad, e.g. if total uncertainty factor is >3,000, then there should be no ESL. Rather it is better to rely on the engineers to use gold standard control technology and minimize emissions. This approach encourages people to generate data. This approach encourages people to generate data.

Other panel members indicated that the SAR discussion was incomplete because it does not indicate what tools will be used to evaluate SAR, nor does it indicate what criteria it will use for assessing how similar a structure must be. TCEQ indicated that Texas A&M University has SAR software and that TCEQ has a cooperative agreement with them to do SAR analysis when needed. Another panel member noted that even closely similar structures have very different toxicological properties. In order to conduct an adequate analysis, one would need to examine multiple chemical structures to define whether the LD_{50} lines are parallel or overlapping. If the lines are not all of equal slope, then SAR will likely not work. Other reviewers felt that the ratio of LD_{50}s

was not a recommended approach, and felt that using the chemical's LC_{50} divided by a large uncertainty factor would be a better approach.

5.7.2 Route-to-Route Extrapolation

One panel member noted that the text describing the limitations of route-to-route extrapolation was an accurate reflection of available guidance documents. However, regardless of the guidance, the approach in the document was still to incorporate a route-to-route extrapolation using conversion of oral doses to inhalation concentrations. TCEQ replied that because they were required by statute to develop ESLs for every chemical, they will use the "dose conversion" approach as a last resort if there are only oral data for a chemical. One panel member noted a flow chart in Gerrity and Henry (1990) would be useful for describing this analysis; however the document needs to describe the criteria for when this "last resort" approach can be applied. This panel member also noted that this approach adds significant uncertainty into the resulting ESL value. One panel member noted that TCEQ needs to evaluate if this approach/step gives the most uncertainty in the overall process - it could be that the dispersion modeling contributes more uncertainty. The document needs to clearly describe this uncertainty, and TCEQ should consider using an additional uncertainty factor when relying on this approach to develop an ESL. Other panel members agreed, noting that the document must state the assumptions and the limitations inherent in this approach if it is used.

Another panel member disagreed that this dose conversion approach should ever be used. This panel member noted that several publications, such as Overton (1990) and Overton and Jarabek (1989a,b) provide equations that give better default parameters for route-to-route extrapolation than using dose conversion. Another panel member agreed, noting that the guidance is not so arduous to ask any toxicologist to consider doing. In addition, using 20 m^3 as the default estimate of respiratory rate is inappropriate because this value does not come close to reflecting a daily ventilation rate that the vast majority of the population can ever achieve.

When faced with a limited data set, the panel discussed which approach was better for developing an acute ESL - using oral data or using an LC_{50}. One panel member suggested using both and evaluating the results. Another panel member stated that using the LC_{50} was a better approach. A third panel member agreed - particularly when the chemical's effect is on the respiratory tract because in that case, oral data are irrelevant. Other panel members agreed, noting that if there is any indication of portal of entry effects, then oral data cannot be used. One panel member noted that the public health is not served when toxicologists develop values based on insufficient data and then assert that the value is health protective. It would be better to state that there are no data and regulate the compound based on management or engineering bases.

One reviewer indicated that, despite stating many of the considerations verbatim from the RfC methods regarding its decision strategy to evaluate whether a chemical is a candidate for route extrapolations, this section of the document is unclear as to whether an ReV will be developed if there exists a potential to elicit portal of entry (POE) effects exists for a given chemical in question. This should be clarified; a flow chart would be useful to make the requisite evaluations more transparent. It is especially disconcerting that the section ends with very rudimentary

equations that essentially accomplish only units conversions without any discussion of the attendant uncertainties. To that end and to be consistent with Agency practice in implementation, one reviewer recommended an additional UF when data are extrapolated across routes unless a PBPK or other robust dosimetry model approach is employed.

5.7.3 Generic ESL

The panel discussed the concept of "threshold of regulation" and noted that several organizations such as FDA or NSF use this approach when the data are not available to develop chemical-specific values. For this approach, the organization chooses a threshold value, such as 1 ug/kg-day, and if the level in question is less than this, then no further action is taken. One panel member noted that several States also use this approach for evaluating fence-line concentrations if no TLV is available. However, other panel members noted that any "threshold value" should at least be compared to the LC_{50} for a chemical.

TCEQ noted that they also use this type of approach and have established a bottom line default that is used in the permitting process if no chemical-specific ESL can be developed. Panel members felt that this was a good approach that allowed TCEQ to only have a chemical-specific ESL when there is a good toxicological foundation. However, the panel members suggested that this "generic ESL" be described in the document (i.e., describe that it exists and how it was determined). This will help to improve the overall understanding of the ESL process and show that there is a minimum data standard for developing an ESL. Therefore, the document should describe the minimum standard for developing a chemical-specific ESL and then describe how the "generic ESL" will be used in all cases where the data are too poor to derive a chemical-specific ESL. In addition, the "generic ESL" should be included in the flow charts.

5.8 Uncertainty Factors

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. In addition, the document needs to distinguish between uncertainty factors that address lack of knowledge from factors that represent known variability in parameters. The document should acknowledge that the UF_A and UF_H factors are composed of both kinetic and dynamic subfactors.

One panel member noted that the rationale for the use of an modifying factor in the RfC methods is described erroneously (and differently) stated on pages 27 and 32 in the ESL document – both are incorrect. The modifying factor was not applied in the RfC methods to account for quality of the database or to address other issues. This MF was applied for deficiencies in the quality of the critical study (i.e., the one used as the basis of the POD) such as sample size or exposure monitoring and not for database adequacy, for which there is a UF.

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.

Relative to page 26, line 33, it is important to define the adverse level for each continuous response (see EPA draft Benchmark Dose Guidance document). A 10% response for continuous data may or may not indicate an adverse response; it depends on the effect. The EPA draft Benchmark Dose Guidance document (US EPA, 2000) describes considerations for selecting the benchmark response level for both quantal and continuous data. However, it was noted that several EPA publications (e.g., Dourson et al., 1985) support the concept of a BMR of 10% being similar to a LOAEL for some toxicity test data, if the severity of the effect being modeled is more than minimal.

For the database uncertainty factor, TCEQ must define what is the minimum database needed for both high and low confidence acute and chronic ESLs before it can determine when a database UF is needed. 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.

One panel member suggested that if TCEQ develops an ESL based on oral data, for example an LD_{50}, then it should use an additional UF to account for route-to-route extrapolation.

The ESL document should cite inhalation papers for implication of kinetics and dynamics subfactors. Two references are:

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.

One panel member suggested that UF_S was not needed for acute ESLs but that a UF for use of an LC_{50} is appropriate. Also, this reviewer also suggested that if an LD_{50} is used to derive an acute ESL, then an additional UF to account for route-to-route extrapolation should be used.

The panel then discussed the tables in Appendix H (H-1 and H-2) of the ESL document. In Table H1, justification for UF of 3, the table indicates that using the most appropriate species will justify moving the UF from 10 to 3. However, using the most appropriate species is a given in risk assessment - the most appropriate species should always be selected and does not justify reducing the uncertainty factor. However, other panel members noted that sometimes, risk assessments are done using a less than ideal species. Panel members suggested the types of data that could be used to reduce the interspecies uncertainty factor including data demonstrating little variability between species or chemical-specific mechanistic data that describes species differences. In addition, panel members indicated that Table H-1 lists use of a dosimetric adjustment factor as justification for using a UF of 3 for intraspecies variation. Yet the document indicates that DAF is not being applied for acute ESLs, so the DAF cannot be used to justify UF of 3. One panel member stated that both the UF_A and UF_H are composed of kinetic and dynamic subfactors, so there are data on both kinetics and dynamics for the chemical, then a UF of 1 is justified. If there are data for just one of the subfactors, then a UF of 3 is justified. Another panel

member indicated that a UF of 1 is justified if a well-conducted human study in the appropriate population or a validated PBPK model.

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. Inadequate data are used as rationale in this table but not are defined nor discussed in the document. In column 2, rows 1 and 4, the table lists factors that should be considered in the selection of the appropriate point of departure, but these are not factors that are considered when selecting an appropriate UF. Another panel member noted that the key to selecting an appropriate UF_H is to look at the nature of the population used in the critical study and the nature of the human population to be protected. If these populations are similar then a UF of 1 may be justified, but if they are different, then a UF of 10 may be needed. A reviewer noted that in column 3, the last row, the consideration of metabolic factors is redundant.

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.

5.9 Cumulative Risk

Panel members noted that the document is not clear about what data will be used as input to evaluate cumulative risk, so it is not clear whether the process for evaluating cumulative risk is appropriate. TCEQ replied that air monitoring data will be used to assess whether there is a local problem with specific pollutants. One panel member noted that using a HQ of 0.1 is the approach selected to account for multiple chemicals present at a site. TCEQ replied that this also accounts for multiple sources of a chemical at a single site. Other panel members noted that the document does not distinguish between cumulative risk (risk from multiple chemicals) and aggregate risk (risk from multiple sources of single chemical). One panel member noted that the document refers to exposure to a single chemical (page 6, line 26), however, practically, no one is ever exposed to just a single chemical. Another panel member indicated that the document only describes evaluating the HQ for noncarcinogens and not carcinogens. However, this reviewer noted that this approach seems inconsistent and the non-cancer properties of carcinogenic chemicals also contributes to cumulative risk.

One reviewer noted that accepted risk assessment methods for cumulative risk involves adding the hazard quotient for chemicals with a similar mode of action and then determining if the overall hazard index is less than 1. However, this approach is not appropriate for evaluating chemicals with diverse modes of action or chemicals from different classes. Therefore, the document does not follow accepted methods. Using a HQ of 0.1 can be acceptable as a screening approach, but should not be used when more data are available. Rather, the document should use more accepted methods. TCEQ replied that the selected their approach of using 0.1 HQ because it most fit within how they do air permitting. The purpose for the ESLs is to have a screening tool that permit engineers can use to assess whether the toxicology section needs to review the permit.

One panel member noted that some programs do use the 0.1 HQ as a screening approach, so there is precedent for using this method.

Panel members suggested that TCEQ should clearly articulate the risk management objectives of the ESLs and then describe the risk assessment that will be used to meet the objective. If screening air permits is the only objective, then the 0.1 HQ method is likely OK. However, if TX has risk management objectives that require a more "detailed" risk value, then an approach that considers target organ, mode of action or chemical class is more appropriate. One panel member noted that there are several locations in Texas where exposure to multiple chemicals is common, and the State needs to have a credible process for evaluating these areas. Panel members noted that the TX supplemental report on cumulative risk was useful, but the connection to the document under review was not clear. TCEQ should consider adding some of the information in this report to the ESL method document.

5.10 Exempt Chemicals

The panel evaluated whether certain chemicals listed by TCEQ as exempt from ESL development should, in fact, not be exempt.

One panel member suggested that the document should describe the criteria that were used for considering a chemical exempt from ESL development. In addition, the document should also add the criteria/data that would move a chemical off the exempt list. TCEQ replied that it mostly relied on professional judgment and intended that only chemicals that clearly belonged on the list should be there.

One panel member suggested that welfare be considered when determining which chemicals be exempt from ESLs. For example, CO_2 should not be exempt because it contributes to global warming - a welfare issue. TCEQ replied that regulating CO_2 is a policy issue that is not within its jurisdiction. One panel member noted that some things on the list such as food seasonings and oils could also have an odor threshold. TCEQ replied that if odor threshold data are available, they would develop an odor ESL. One panel member noted that even though lead is regulated by its NAAQS, there may be local situations with high air lead concentrations. Therefore, TCEQ may want to develop an ESL to address local issues.

Other reviewers asked whether TCEQ regulated chemicals, such as methane, that are ozone generators. TCEQ replied that other State programs regulate this issue. Panel members suggested that the document should indicate when a chemical is on the exempt list because it is regulated by another program without an explanation or presentation of the rationale for being exempt from ESL development, Appendix E as currently provided seems inadequate. Certainly carbon dioxide, known as a displacement toxicant and used for euthanasia, can not be considered without adverse effects in laboratory animals or humans. Effects of CO_2 in the atmosphere are also well documented and seem to warrant consideration under "welfare". Hydrogen and nitrogen can be very toxic to vegetation. Methane, ethane, and propane likewise present explosive hazards.

5.11 Odor/Acute Effects

The panel discussed the approaches to setting odor ESLs described in the document and suggested alternative acute endpoints that are more closely tied to health effects than odor.

Panel members noted that the potential for perturbation of the epithelium by corrosion or oxidative damage and for narcosis or other CNS effects from gases such as solvents are of a greater toxicological concern than perception of an odor and considerations of data suggestive of these types of effects may be more relevant as the basis of ESLs. One reviewer stated that the biggest concern for acute exposure levels are the potential for chemicals to be immediately corrosive, directly damaging or irritating. This reviewer suggested that any chemical with a "skin" notation or a short-term STEL designated either by the ACGIH or NIOSH should be considered with additional scrutiny as these flags clearly signal the potential for corrosive or directly damaging effects. This is a mechanistic consideration that should and include it in the decision flow chart to enhance the ESL MD guidance.

The rationale for the choice of 50% detection threshold should be explained. Reviewers noted that there is not a good toxicological basis for establishing screening levels based on odorant properties, especially because the ability to detect or perceive an odor does not typically map with levels associated with toxicity. In addition, panel members were concerned about the variability of these data and suggested that the document should include more text devoted to what attributes help standardization of testing. In addition, panel members note that cognitive issues are involved with odor perception TCEQ replied that odor perception is an important factor to consider when working with the public, since the public tends to believe that if they can smell a chemical, it must be harmful. In addition, a different panel member noted that there areas in Texas where the odors from multiple chemicals are so bad, that one cannot breathe. People would take action to cover odor, such as increased use of deodorizers which may also have harmful effects. Therefore, odor should not be dismissed. The largest number of complaints received by the city health departments is about odor problems. In addition, another panel member pointed out that in areas where agencies receive regular complaints of odor, people also have other health symptoms.

One panel member suggested that the databases on sensory irritation potential should be considered rather than odor perception as the basis of acute ESLs. Several panel members suggested that the exposure concentration that results in a 50% reduction in respiratory rate in rodents (typically mice), or the RD_{50} (Kane et al., 1979; ASTM, 2000) would be a more relevant basis for an acute ESL than odor. The RD_{50} has been suggested to have a predictable relationship to irritation in humans (Kane et al., 1979) and different fractional concentrations of the RD_{50} have been suggested to correspond to industrial and environmental standards, e.g., a concentration of 0.1, 0.01 and 0.001 times the RD_{50} were proposed to relate to the highest acceptable TLV concentration, the lowest necessary TLV concentration, and highest concentration for an ambient air standard (Kane et al., 1979). Reviewers also noted that a much larger database is available for RD_{50}s than that cited in the ESL for odor thresholds. However, a different panel member questioned whether the dose-response of this effect had been quantified in humans. Other panel members responded that the human response is qualitatively similar and quantitatively different than mouse response, but that the RD50 can be well correlated between the two species. They

noted that the value is just an index, and that it is most relevant to the reactive gasses and not relevant for amines or the narcotic effect of solvents.

The panel also discussed the issue of sensitization, with one panel member noting that document is not clear as to whether or not sensitization per se or exacerbation of existing asthma is the basis of acute ESLs. This should be clarified as the distinction has important implications for the types of data to be considered and how to address data gaps. This panel member noted that sensitization has a role in the development of immune type asthma. High concentrations of some chemicals such as isocyanates actually result in an immunological sensitization, while other chemicals appear to make the respiratory tract more sensitive following exposures, but without an immunological component. Another panel member noted that asthma was a syndrome rather than a single disease process. TCEQ replied that it intended to look at sensitization. Panel members suggested that the ESLs should protect the population from sensitization, but not necessarily protect already sensitized individuals. This is the current practice of other federal and state agencies.

5.12 Mixtures

In general, panel members felt that the approaches described for mixtures assessment were appropriate. One reviewer stated that PAHs and dioxins are formed in the environment after emission, rather than in the stack where they are measured and asked how TCEQ addressed this phenomenon. TCEQ replied that it was a complex issue that no one has addressed yet. One panel member noted that a group at the University of California at Riverside is doing research to develop a model that will address the issue, but at this point there is no approach for dealing with this issue other than specific control measures for emissions. Another reviewer agreed that management practices are the only approach for dealing with this issue, and suggested that literature dealing with prevention of significant deterioration could provide some information.

One panel member asked if stack emission testing speciated PAHs. TCEQ replied that they received data for about 16 PAH. Another panel member indicated that PAHs are present only on the surface of particles and that this called for a different dosimetric adjustment.

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. For non co-planar dioxins and PCBs, it is more appropriate to use EPA's PCB assessment.

5.13 Policy

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.

5.14 General Recommendations

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. Other panel members suggested that the document would be strengthened by the use of more graphics to illustrate key points. For example, a graph that illustrates the point of departure within the range of observation and then the various approaches (e.g., nonlinear or linear or both) to extend into the range of extrapolation would clarify the discussion on point of departure.

One panel member suggested that some of the terminology is inaccurate. For example:

- *Systemic toxicity*. It is inaccurately stated that RfC addresses systemic toxicity – almost 70% of RfC derivations are based on portal of entry (POE) toxicity.
- *Linear carcinogen*. The evidence should be evaluated as to whether the mode of action (MOA) for a carcinogen is likely to be linear or nonlinear. Both are carcinogens.
- *Mutagenic carcinogen*. This is used in the document to suggest a linear carcinogen, yet many mutagenic chemicals have nonlinear modes of action.
- *Particulates*. Particulate is an adjective and not a noun. These exposures and adjustments are for particles, not particulate.

Another panel member suggested that "welfare" be better defined and addressed by the document. In addition, the approach should also consider ecotoxicology. TCEQ replied that they will consider addressing ecotoxicology issues when better guidance is available. Another panel member noted that the NAAQS criteria documents have approaches for dealing with welfare, vegetative effects, and ecotoxicological issues that could be incorporated into the ESL methods.

Panel members noted that, based on the presentation and answers by TCEQ, their understanding of TCEQ's process has changed. One panel member noted that the flow charts were constructed so that it was possible to reach inappropriate dead ends. In addition, the figures do not accurately reflect TCEQ's process and should be redrawn to include a step for evaluating available data and existing values.

Several panel members noted that the cancer pathway in Figure 2 only allows for derivation of an ESL based on a linear mode of action. One panel member suggested that Figure 2 should also include a pathway that allows for a nonlinear cancer mode of action. However, a different panel member suggested that rather than adding a separate pathway, Figure 2 should be revised so that the output of a cancer dose response assessment is a risk value that is based on either a linear (URF) or nonlinear (ReV) extrapolation. In either case, the panel agreed that the figure should include steps for considering database criteria, physicochemical characteristics of chemical in question, MOA analysis and determining if linear or nonlinear dose response is most appropriate. This will help readers understand that the data, rather than the ready-made risk estimates, will drive the derivation of ESLs' by TCEQ. Also, reviewers noted that some pathways in the flow charts ended without having a final action and suggested that the flow charts be reorganized. (See also additional discussion under Sections 5.2, Hierarchy, and 5.5, Cancer assessment).

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.

Several panel members suggested that the document should describe what mechanisms the TCEQ has in place for external scientific peer review of its proposed ReVs, including how the availability of the draft estimates will be announced and what provisions will be used to address conflict of interest of the future reviewers. The scientific peer review should also be representative of all perspectives (business, government, public, and academic).

One panel member suggested that TCEQ not use roman numerals for numbering sections in document, because this numbering system was confusing.

One panel member suggested that the document provide more description of the hazard characterization process in this chapter. This panel member also suggested avoiding the term "noncarcinogen". The panel observed that what is pertinent to this document is the differentiation in the foundation for the two different types of values derived for consideration in setting an ESL (i.e., the reference value and the cancer unit risk factor). Cancer unit risk factors are derived for all substances concluded to be carcinogenic and assigned a linear dose-response (either via science policy default or as supported by chemical-specific data), while reference values are developed for all chemicals (carcinogen or not) based on an identified "critical effect", which may in fact be cancer (if it has been determined that the dose-response relationship for this chemicals elicitation of cancer in humans is non-linear).

One panel member suggested reorganizing the document so that all of the issues that are common to both the acute and chronic ESLs are included in Chapter 2, for example, BMCL, uncertainty factors and dosimetry. Then Chapters 3 and 4 can focus on issues that are unique to development of acute and chronic ESLs.

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 Page 9. Therefore, this section should be expanded to encompass current scientific data on assessing plants. 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. Further, it is not clear why vegetation effects are not considered for chronic characterization.

6. Summary

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.

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. 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.

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.

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.

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.

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.

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 that chronic exposures.

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. Suggestions regarding approaches to limited data include:

- 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.
- 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.

- Applying the ratio of LD_{50}s is not recommended for assessing inhalation exposures.
- 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.
- If route-to-route extrapolation is used, consider applying an additional UF.
- The document should describe the "generic" ESL applied by TCEQ.

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. Some specific suggestions regarding uncertainty factors include:

- Consider only modeling benchmark responses of minimal severity before determining whether an uncertainty factor for LOAEL to NOAEL extrapolation is needed.
- Define the database criteria for acute and chronic ESLs.
- Apply an UF if an LC_{50} is used as the basis of an acute ESL.
- Consider an additional UF if route-to-route extrapolation is used as the basis of an ESL.

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. The document should develop HQs for the noncancer properties of carcinogens and consider them in the cumulative risk assessment.

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. 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.

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. 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.

Panel made several general recommendations of an editorial/organizational nature including:

- 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.
- Terminology - clarify and update terminology used in order to be more consistent with U.S. EPA guidelines.
- Define "welfare" and consider including approaches from NAAQS that deal with welfare issues
- 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.

7. References

ASTM (American Society for Testing and Materials). (2000). Standard test method for estimating sensory irritancy of airborne chemicals. In Annual Book of ASTM Standards. Designation E981(Reapproved 2000). American Society for Testing and Materials, Philadelphia, PA.

Bogdanffy MS and Jarabek AM. (1995). Understanding mechanisms of inhaled toxicants: Implications for replacing default factors with chemical-specific data. Toxicol. Lett. 82/83: 919-932.

Clewell HJ; Gentry PR; Covington TR; Sarangapani R; Teeguarden JG. (2004). Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. Toxicol Sci. 79(2): 381-393.

Dietert RR; Etzel RA; Chen D; et al. (2000). Windows of Vulnerability for the Immune and Respiratory Systems. Environ. Health Perspect. 108(Suppl. 3): 483-490.

Dourson ML; Hertzberg R; Hartung R; Blackburn K. (1985). Novel methods for the estimation of acceptable daily intake. Tox. Ind. Health. 1: 23-33.

Dourson ML; Charnley G; Scheuplein R. (2002). Differential Sensitivity of Children and Adults to Chemical Toxicity: II. Risk and Regulation. Regul. Tox. Pharmacol. 35: 448-467.

Gerrity TR and Henry CJ. (1990). Principles of Route-to-Route Extrapolation for Risk Assessment. Elsevier, New York. p. 322.

Ginsberg G; Slikker W Jr; Bruckner J; Sonawane B. (2004). Incorporating children's toxicokinetics into a risk framework. Environ Health Perspect. 112(2): 272-283.

ICRP (1994). Human respiratory tract model for radiological protection. ICRP Publication 66. Permagon Press, International Commission on Radiological Protection. p. 482.

Jarabek AM. (1995a). The Application of Dosimetry Models to Identify Key Processes and Parameters for Default Dose-Response Assessment Approaches. Toxicol. Lett. 79: 171–184.

Jarabek AM. (1995b). Interspecies Extrapolation Based on Mechanistic Determinants of Chemical Disposition. J. Human Ecol. Risk Assess. 1(5): 641–662.

Jarabek AM. (1995c). Consideration of temporal toxicity challenges current default assumptions. Inhal. Toxicol. 7: 927-96.

Jarabek AM; Asgharian B; Miller FJ. (2005). Dosimetric adjustments for interspeicies extrapolation of inhaled poorly soluble particles (PSP). Inhal. Toxicol. 17: 317-334.

Kane LE; Barrow CS; Alarie Y. (1979). A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40: 207-229.

Miller FJ; Schlosser PM; Janszen DB. (2000). Haber's rule: A special case in a family of curves relating concentration and duration to a fixed level of response for a given endpoint. Toxicology 149: 21-34.

Overton J and Jarabek A. (1989a). Estimating Human Equivalent No Observed Effect Levels for Vocs Based on Minimal Knowledge of Physiological Parameters. U.S. Environmental Protection Agency, Washington, DC. EPA/600/D-89/097 (NTIS PB89224588).

Overton JH and Jarabek AM. (1989b). Estimating equivalent human concentrations of no observed adverse effect levels: a comparison of several methods. Exp. Pathol. 37: 89-94.

Overton JH. (1990). Respiratory tract physiological processes and the uptake of gases. In: Principles of Route-to-Route Extrapolation for Risk Assessment. Eds. Gerrity TR and Henry CJ. New York, Elsevier Science Publishing Co., Inc. p. 71-91.

Snipes MB; James AC; Jarabek AM. (1997). The 1994 ICRP66 human respiratory tract dosimetry model as a tool for predicting lung burdens from exposures to environmental aerosols. Appl. Occup. Environ. Hyg. 12(8): 547-554.

US EPA (United States Environmental Protection Agency). (1994). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-90/066F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993.

US EPA (United States Environmental Protection Agency). (2000). Benchmark Dose Technical Guidance Document, External Review Draft. Risk Assessment Forum, Washington, DC.

EPA/630/R-00/001. Available at: http://www.epa.gov/nceawww1/pdfs/bmds/BMD-External_10_13_2000.pdf.

US EPA (United States Environmental Protection Agency). (2002). A Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum, Washington, DC. EPA/630/P-02/002F. Available at: http://www.epa.gov/iris/RFD_FINAL[1].pdf.

US EPA (United States Environmental Protection Agency). (2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001B. Available at: http://www.epa.gov/iris/cancer032505.pdf.

WHO (World Health Organization). (1987). Air Quality Guidelines for Europe. 2nd ed. WHO Regional Publications, European Series, No. 91. Available at: http://www.euro.who.int/document/e71922.pdf.