Report of the Peer Consultation Meeting on a Draft Framework To Evaluate Whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children

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Kingsgate Conference Center
University of Cincinnati

Peer Consultation Organized by
Toxicology Excellence for Risk Assessment
(http://www.tera.org/peer/)

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Table of Contents

Executive Summary

An expert panel was assembled on March 31, 2005, to conduct a scientific peer consultation of a document titled the "Draft Framework to Evaluate Whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children." The document and background information discussed at this peer consultation were prepared by scientists from *TERA*. The panel held in-depth discussions regarding key aspects of the document as highlighted in the charge to the panel (found in Appendix B of this meeting report). The deliberations of the panel were supplemented by input from the document authors and meeting observers.

The meeting began with the document authors summarizing the framework document. They stressed that although the ideal approach to dosimetry is a PBPK model, their goal was to develop a physicochemical property-based approach for evaluating dosimetric differences when there are insufficient data, time, or resources to develop a PBPK model. They presented schematic diagrams of conceptual frameworks for particles and also for gases and vapors, explaining that the frameworks were based on the assumption of steady-state.

Following the authors' presentation, panel members asked clarifying questions and made general statements regarding the intended scope and ultimate use of the document. The panel then addressed the panel charge, which consisted of questions provided to them prior to the meeting.

The first several charge questions related to the framework for particles. The panel divided its discussion of this framework into five areas: the implications of using deposited dose to estimate lung burdens for particles, the time-weighted averaging approach for estimating age-dependent deposited dose ratios, the consistency of the approach with RfC methodology and opportunities to use alternative models, considerations of dose metrics and extrarespiratory (systemic) effects, and suggested revisions to the configuration of the framework for particles.

During their discussion of the framework for particles, panel members discussed numerous complications regarding assumptions of steady-state lung burdens inherent in descriptions of deposited dose as the dose metric, and they emphasized the importance of considering duration issues in the framework. They identified a key consideration as being how to evaluate risk over a lifetime based on age-specific kinetics. The panel also discussed the approach used for considering extrarespiratory effects of particles and listed several key points for the authors to consider. In addition, they reviewed the schematic diagram of the overall configuration of the framework for particles and suggested a number of modifications to improve clarity and completeness.

The panel then discussed the charge questions related to the framework for gases and vapors. In discussing this framework, the panel said it was generally appropriate to use the RfC methods with reliance for the default descriptions on partition coefficient ratios and steady-state equations; however, the work of all the investigators in this area regarding derivation of values for partition coefficients should be included in the document for completeness. They noted that substantial differences in partition coefficients between children and adults have been reported in the literature and suggested that these differences be highlighted in the document. The panel discussed how steady state applies to human equivalent concentration calculations and whether

the RfC approach used to extrapolate from the laboratory animal to the adult human adequately accounts for steady state. They noted that the dosimetry adjustment to human equivalent concentration is not intended to be inclusive of the consideration of child versus adult kinetic differences but is rather under the purview of uncertainty factor (UF) applied for intrahuman variability.

They further noted that using the proposed framework for acute values raises a concern since it is unlikely that a child will have reached steady state. Panelists recommended providing an analysis using two limiting cases: (1) for long-term exposure use steady state equations, and (2) for short-term or acute exposures use ratios based on chemical uptake. Because blood flow limitation is a critical consideration, they thought the document should be clear how blood flow can impact the analysis. They recommended that the document include examples of blood flow-limited metabolism in an adult and in a child as bounding cases. They also suggested discussing the implications of blood flow to the liver, since blood flow limitations could quench age differences in metabolic rate. The impact of extrahepatic metabolism also was discussed.

The panel asked whether parent compound should be considered more than metabolites in acute exposure situations. While metabolites can be relevant for acute exposures, most panelists concluded that for acute exposures where the metabolite was the active form, chemical specific data or a PBPK model should be used to assess age-dependent kinetics. They discussed using the framework for long-term exposure for a toxic metabolite and concluded that including reactive metabolites in the framework is feasible using bounding estimates based on maximum extraction by metabolism and on flow-limited metabolism in both adult and child.

The panel discussion on the gases and vapors framework led to several modifications, which are presented as the "Revised Framework for Particles" in Section 7 of this meeting report.

Other considerations identified in the charge to the panel also were addressed. One of these was whether a separate framework should be developed for oral exposures or whether oral exposures could be incorporated into the current framework. In general, panel members thought that a similar analysis for oral exposures would be of value and is feasible, but that it should be done as a different framework in a separate document. They advised preparing a specific oral document because consideration of ingestion requires additional specific parameters such as GI transit time.

Several approaches for evaluating and testing the sponsor's framework were discussed. Most panelists agreed that comparing the framework results and their supporting analyses to the analyses of others would serve as a reality check and would provide an opportunity to investigate the sources of any discovered differences.

In summary, the panel discussed the framework document in depth and identified a number of data gaps regarding age-dependent differences in toxicokinetics. They considerably revised the original framework, noted some uncertainties in understanding adult-to-child differences that were not addressed in the framework, and suggested additions and clarifications.

1. Participants

Presenters

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Observers and Other Attendees

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

2. Background

This peer consultation meeting has been 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 peer consultation meetings for private and public sponsors since 1996. *TERA* is further developing the peer consultation concept with various projects, particularly those evaluating risks to children such as the Voluntary Children's Chemical Evaluation Program (VCCEP) and this consultation on the "Draft Framework to Evaluate Whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children." The draft framework and background information discussed at this peer consultation were prepared by three scientists from *TERA*. To maintain separation and independence between the development of the work product and the peer consultation panel meeting to evaluate the work product, *TERA* scientists other than the authors were responsible for organizing the panel meeting (i.e., selecting panelists, developing panel charge, preparing this report).

The peer consultation panel for this meeting consisted of 8 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases related to the authors or to the subject matter of the submission. *TERA* evaluated these disclosures before selecting the panel members, and the disclosures were publicly presented at the beginning of the meeting (see Appendix B for the panelist disclosure statements). The panel members were experienced in various disciplines, including dosimetry and physiologically-based pharmacokinetic (PBPK) modeling, toxicokinetics, inhalation toxicology, risk assessment and children's health. The panel members received a copy of the submission document and key references approximately one month before the meeting to provide them with adequate time to review the documents and prepare for the discussions. During the peer consultation panel meeting, the panel members did not attempt to reach consensus opinions; instead, the opinions expressed by the individual panelists were summarized for this report.

Members of the public were invited to attend the peer consultation meeting and were given the opportunity to provide brief oral or written technical comments on the submitted materials.

This report summarizes the authors' presentations and comments, the panel discussions, and comments from the public. The meeting report is a summary, not a transcript. Furthermore, this report does not restate the technical details provided in the submission, and for this reason, to understand the context of some panel comments the reader will find it useful to review of the submission. Panel members reviewed and commented on the draft report. The authors also reviewed the draft report to confirm the accuracy of their presentations and comments. This report is available to the public on the Internet at http://www.tera.org/peer/adultchildtk/actkwelcome.htm.

This report is organized into sections corresponding to the charge questions addressed by the panel.

3. Introductions, Conflict of Interest, and Meeting Process

The meeting opened with a welcome by Dr. Dan Briggs of *TERA*. He described the background and purpose of the peer consultation and explained that this panel was convened at an early stage of development to offer suggestions and to provide guidance. He 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 indicated whether they had additions or changes in their disclosure statements. No panelists had changes or additions.

Dr. Briggs explained that three *TERA* scientists prepared and sponsored the submitted materials for this peer consultation, while other *TERA* staff selected the panel members, prepared the Charge, organized the meeting, and would prepare the meeting report. *TERA* maintained a separation between these two groups to assure that the authors did not influence the panelist selection or the conduct of the consultation meeting.

Ms. Jarabek, the panel chair, described how the meeting would be run. She explained that discussions would be based on the items found in the Charge to the panel (located in Appendix B). She 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. No attempt would be made to reach consensus positions on the charge items. The chair reminded the panel that the purpose of the peer consultation was not to critique the submission *per se*, but to provide guidance and suggest improvements.

4. Author Presentation

Mr. Eric Hack of *TERA* provided a brief overview of the draft framework. The presentation gave a summary of the framework, supporting dosimetry calculations, conditions under which the framework is and is not applicable, and several suggestions for further refinement through future research. Mr. Hack stressed that while the ideal approach to describe dosimetry is a PBPK model, the authors' goal was to develop a physicochemical property-based approach for evaluating dosimetric differences when there are insufficient data, time, or resources to develop a PBPK model. It was noted that the framework was not designed to evaluate toxicodynamic differences, fetal toxicokinetics, reproductive and developmental endpoints, or differences in exposure patterns. Mr. Hack presented a schematic of the conceptual frameworks for particles and for gases. He noted that the framework would be applicable for acute exposure scenarios or when the exposure duration is relatively short compared to the length of the life stage or a window of susceptibility. Mr. Hack also explained that the draft framework was based on the assumption of steady-state and was not appropriate for evaluation of compounds which take an extremely long time to reach steady-state levels in the body. The authors commented on numerous potential enhancements to the framework and key

areas that could be further explored and incorporated into the approach were noted, including intra-age variability, alternative inhalation dosimetry models, age-specific lung clearance rates, consideration of Category 2 gases, systemic kinetics of deposited particles, additional supporting bounding estimate calculations, extrahepatic elimination, an oral exposure pathway, non-steady-state kinetics, and more generalizations drawn from chemical-specific analyses using PBPK models.

5. Panel Discussion

5.1 Clarifying Questions and Overall Framework Considerations

Many of the panel's clarifying questions and initial statements pertained to the intended scope and ultimate use of the document. They included both general issues that applied to the entire framework (presented immediately below in this section) and issues that were specific to either particulates or to gases and vapors (presented in subsequent sections). The general issues included such items as (1) the context for the use of the document was not provided. Specifically there is the need for more clarity of the document's intent, scope of covered chemicals, and intended audience; notably more transparent distinction between age-adjustment of the dosimetry estimates per se versus consideration of age differences when assigning an uncertainty factor (UF) for intrahuman variability, (2) the need to discuss the distinctions between variability and uncertainty and the implications of these two different concepts for assigning UFs, (3) the importance of correct parameter selection when comparing adult and child kinetics, and (4) the appropriateness of including reproductive and developmental toxicity endpoints in the proposed framework.

Responding to comments from several panel members that the document's intent and intended audience were not clear, the authors explained that their intent was (1) to provide guidance to risk assessors on how to evaluate human kinetic variability between children and adults and (2) to aid in identifying cases where applying an adjustment factor of 3.2 to account for human kinetic variability (as described in IPCS, 2001) is or is not likely to be adequate to protect children. The authors further noted that in developing this guidance, they built on the analyses of others and conducted additional analyses of their own. In further discussions of this point, one panelist said the document was organized more as a scientific paper than as a guiding framework, while several others suggested reorganizing to present the framework diagrams first, followed by the detailed analyses.

Panelists thought the framework document should acknowledge that the guidance might change with new data and with updated models. They thought communicating the current analysis to the scientific community may encourage other parties to collect data or suggest enhancements to the approach. Consistent with this concept, several panel members suggested additional reference materials, models, and sources of data for the authors to consider in revising the framework document. These additional materials are referenced throughout this report in the context of the specific discussions of the panel.

Two panelists recommended taking example chemicals through the framework to determine whether it provides sufficient guidance. If it does not, then the use of modeling or uncertainty approaches may be required. Another panelist suggested using quantitative structure activity relationships to fill data gaps when running example compounds through the framework. Panelists said they were unclear whether the framework document was intended to cover only a certain range of compounds, and they noted that if the intent is to include compounds with long biological half-lives, then the framework needs to consider additional factors.

The panel emphasized the need to be clear about the difference between the considerations of variability in dose metrics due to age differences and the application of factors to account for uncertainty. One panel member thought the implications of variability were not adequately developed in the document. Making judgments about whether an uncertainty factor is sufficient involves risk management decisions requiring additional targeted analyses beyond those presented (e.g., evaluation of the adequacy of the database has implicit considerations of whether all life stages have been sufficiently tested; concern for systemic toxicity is less when portal of entry effects are likely to be sentinel, etc.). The document's use of measures of central tendency to compare an average child to an average adult was a concern if the authors intended to use these results to make judgments about UFs for human variability. Furthermore, identification of cut points for defining groups of concern is not appropriate in the absence of an evaluation of human variability. While acknowledging the inability of the current analysis to evaluate variability, another panelist responded that a focus on central tendency is appropriate for the purposes of comparing differences in kinetics between adults and children. Other panel members suggested that instead of picking a specific ratio (calculated from the value of the selected parameter in children to that of adults) to identify groups of concern, it would be better to identify a reasonable range and distribution for data from different exposure and sample populations and to be explicit about the implications of the range for risk assessment. Another panelist thought the proposed approach was appropriate if the intent was to parallel the current EPA guidance on derivation of inhalation reference concentrations (RfCs) (US EPA, 1994); however, in the future, the framework might be expanded to include consideration of variability. Others added that evaluating numerous sources of variability in models is important to determine the parameters to use for evaluating the central tendency in children versus adults. The distribution of means across studies can also provide valuable information on variability.

Other members cautioned that many issues must be considered when selecting critical parameters for evaluating age-related differences such as enzyme affinities (i.e., K_m values); therefore, selection of parameter values from a range should not be based only on risk management. Parameter values can vary across studies due to many factors such as the types of measurements, and the variance of mean parameter values can provide valuable information on parameter value distributions. The document should recognize the importance of selecting the correct parameters for comparing children versus adult kinetics, but this document should not be a guide for doing this. Furthermore, the

importance of including the dose metrics (not just the ratios) should be emphasized, since even a high ratio for some parameters may not be biologically meaningful if the absolute dose difference between children and adults is low. Several panel members believed the framework can give advice based on central tendency, and it also can indicate issues and provide guidance for different approaches for incorporating variability information.

The panel discussed distinctions between concepts of age-specific dosimetry versus the use of these differences to assign UFs. One member noted the document is trying to address two issues at once in comparing children and adults by combining concepts of both dosimetry and uncertainty. This panelist thought the suggested approach of using central tendencies is good if it is made clear that the intent is to characterize dosimetry. Another member was uncertain if the ratios for the regional deposited dose ratio (RDDR) presented in the document were intended to be calculated as in the EPA RfC guidance (US EPA, 1994) or were inverted to be presented as a parallel to the International Programme on Chemical Safety's (IPCS, 2001) chemical specific adjustment factors for toxicokinetics. Others recommended presenting the ratios as dosimetry ratios consistent with the RfC guidance to maintain separation of dosimetry and UFs. Members agreed that both approaches might be presented in the document, but it must be clear whether the calculated number reflects the RfC equation for dosimetry or has been inverted to serve as a comparison for the IPCS approach. This discussion highlighted the need to clarify the context of the document and to specifically note the relationship between dosimetry adjustment in derivation of a human equivalent concentration (HEC) and subsequent consideration of variability and uncertainty when assigning the UF to account for human variability.

Panelists recommended the framework document be explicit about separation of the concept of dosimetry from that of selecting UFs and be clear on the implications of the metric selected for analysis. The level of biological organization that the metric represents needs to be considered (e.g., enzyme system versus whole organism) when evaluating the degree to which the selected comparison covers other sources of age-dependent kinetic differences. For example, a panelist asked whether the calculated ratio should be seen as an intake adjustment factor or as a ratio covering all aspects of toxicokinetic variability. It was further discussed that the document does not address how to apply the framework when the quantitative ratio suggests a value of less than 3.2 (i.e., children may not be of special concern based on the selected parameter), but the qualitative information indicates that there is greater concern for a child than for an adult. This panelist noted that in some cases a child:adult ratio may be adequately addressed as part of other sources of variability. On the other hand, although a ratio calculated from a specific parameter may be less than the default factor, other parameters might be drivers for increased susceptibility in children. Since it is unclear whether the differences represented by the calculated ratio are additive with other sources of age-dependent kinetic differences, it is important to explore the basis for variability. If the variability within different age groups is caused by the same kinetic parameter, then it is more likely that the ratio based on this parameter accounts for child:adult differences.

Several panel members noted that endpoints related to reproductive and developmental toxicity were excluded from the framework. They thought it was unnecessary to constrain the framework in this way. A panelist added that exclusion of these endpoints by the authors might indicate that, if the data were available for developmental toxicity endpoints, the effect level for the critical life stage of interest would already be known. A second panelist added that, if that were the case, extrapolation from adult-to-child would be accounted for in the selection of the critical effect. This panel member also noted, however, that the FQPA (Food Quality Protection Act) includes the fetus in the definition of a child, which suggests that inclusion of developmental toxicity endpoints from *in utero* exposure would be an appropriate consideration in evaluating child versus adult kinetics in this framework. Others commented that the issue of whether endpoints have been assessed for reproductive or developmental effects is addressed in the database UF and is not germane to determining the magnitude of the UF for kinetics, but age-specific extrapolation of different life stages is being done more frequently for determination of the HEC. Risk assessments often must consider exposure situations for *in utero* versus postnatal exposures for the same compound, and the relevant kinetic considerations could be different (e.g., with lead and with mercury). Thus, the framework should leave open the possibility to include *in utero* considerations. Another panel member suggested including developmental endpoints, but not necessarily always including reproductive effects, since some reproductive endpoints would not be relevant to exposures to children. Resolution of the scope of endpoints is required in any future documentation.

5.2 Discussion of Framework for Particles (Charge Questions 1 to 6)

The panel discussed at length the organization of the framework for particles. Key discussions surrounded (1) the implications of using deposited dose to estimate lung burdens for particles, (2) the time-weighted averaging approach for estimating age-dependent deposited dose ratios, (3) consistency of the approach with RfC methodology and opportunities to use alternative models, (4) considerations of dose metrics and extrarespiratory (systemic) effects, and (5) overall changes to the configuration of the framework for particles. Discussion of each of these topics is summarized below.

5.2.1 Implications of Using Deposited Dose to Estimate Lung Burdens for Particles

In considering exposure to particles, several panel members noted complications regarding assumptions of steady-state lung burdens inherent in the deposited dose approach used by the sponsors. They noted that duration issues are important in evaluating the framework because considerations for acute exposures will be different from those used in the RfC approach for longer-term exposures. For example, based on intermittent exposure patterns, real exposures are unlikely to generate steady-state body burdens. In addition, activity levels for children are different from adults and equilibration times will differ; therefore, the framework will almost never be applied to consistent steady-state conditions across age-groups. One panel member noted that achieving steady state is not a determinant of the toxic effects of all chemicals. For example, local tissue damage may give rise to pulmonary effects due to non-steady state exposure conditions. This consideration leads to the need for a different kind of analysis

than the analysis approach that was done in support of the proposed framework, based on the deposited dose in the lung. Another panelist noted that evaluating steady state in the lungs is complicated because of its dependence on deposition site and local kinetics. For example, a particle may be cleared in minutes from the tracheobronchial region, but it may be retained in the pulmonary region for months. Other members noted that the definition of steady state needed to include evaluation of critical life stage. One such criterion could be rapid attainment of steady state within a certain time frame as done in the RfC methods (i.e., at steady state for at least 90% of the time period of concern). However, in general, the use of steady state approaches is most relevant for issues of chronic exposure and does not consider life stage or pulmonary issues adequately. The definition of steady state should be left open in the document with an explanation of the importance of defining the term for each chemical as it relates to the life stage of concern. It was acknowledged that in real exposure situations steady state may never be reached because exposures are usually intermittent.

The appropriateness of using deposited dose for assessing age-specific kinetic differences depends on the importance of particle clearance for the exposure scenario and the toxic effect of interest. Deposited dose may be an appropriate metric for acute exposure whereas retained dose is more relevant for chronic exposures (Dahl et al., 1991; Bogdanffy and Jarabek, 1995). This point was discussed in detail by the panel. Several members thought it was critical to consider particle clearance in evaluating age-specific doses, since clearance affects the tissue dose; however, they noted that differences in lung clearance by age have not been well-studied. One member said the only data he was aware of (Ginsberg, 2005) showed age-dependent changes in nasal mucous flow. Another panelist cited data for age differences in tracheobronchial clearance (Jarabek et al., 2005).

Another member noted a manuscript (Bohning et al., 1982) on the clearance rate of radio-labeled polystyrene particles from the pulmonary regions of adult smokers versus non-smokers. This paper likely provides data on human variability in particle clearance, but the results would not include children. Panel members agreed the framework should start with the consideration of clearance (based on what is known for a given chemical) before moving to the default approach of using deposited dose; however, they acknowledged that in most cases there will not be data on age-dependent differences in clearance. Furthermore, age-specific considerations of clearance are complicated by the presence of multiple mechanisms for particle clearance (including particle dissolution, mucociliary clearance, and macrophage engulfment with transport to the lymph system).

Issues and approaches for incorporating particle clearance considerations in the framework were discussed by the panel and post-meeting clarifications were also provided and are reflected in this summary. Insoluble particles can be adequately described primarily by physical clearance rates (e.g., mucociliary rates). While these rates have been determined in adults, the dimensions of the airways in children preclude their application with certainty to other age groups. Further, there may be age-specific aspects of the physical clearance rate. One panel member commented that soluble particles generally have insufficient data to develop a quantitative estimate of differences

in retained dose because calculation of clearance requires description of both physical transport and chemical solubility in addition to initial deposition. Assumptions of dissolution rates have been shown to be one of the most sensitive parameters in calculating retained dose of particles (Snipes et al., 1997). Another panelist noted that the use of deposited dose is a good start and preferred over no dosimetric adjustment at all, but that clearance of insoluble particles also should be considered whenever possible to calculate retained dose.

Soluble particles often will have data on clearance via dissolution, but careful consideration of the types of measurement and conditions (e.g., in vitro or in vivo) is required. Highly soluble particles could present less concern for age-dependent differences in clearance rates. Estimates of retained doses of highly soluble particles can be bounded based on consideration of their solubility. Effects of solubility on radionuclide clearance have been studied using the International Commission for Radiological Protection (ICRP) model, and this work might provide insights useful for including this consideration in the framework (Snipes et al, 1997; Bailey et al., 2003a). Further, an international effort is underway to catalog solubility parameters of various chemicals for use in the ICRP model (Bailey et al., 2003b).

Other ideas to inform the consideration of particle clearance also were suggested. Both the ICRP and the Multiple Path Particle Dosimetry (MPPD) models include clearance parameters, and these models might provide bounding estimates of the impact of clearance on child versus adult lung dose. One panelist suggested describing this issue in more detail in the text, but he thought that running models may not be appropriate since the models will be sensitive to clearance, for which age-specific data do not exist. An observer asked if the panel could expand on the alternative ICRP and MPPD models. The chair explained that the ICRP model is a semi-empirical compartmental model that describes deposition and clearance as an average estimate for the major respiratory tract regions (extrathoracic, tracheobronchial and alveolar) of a Weibel-type lung structure (Weibel, 1963). Deposition is calculated based on particle size and distribution. Clearance is estimated as a function of physical transport via the mucociliary escalator, dissolution, and lymphatic drainage. Rather than an average estimate using a typical-path description, the MPPD model provides for stochastic input, adjusts for ability to be inhaled, and can calculate based upon either “single-path” and “multi-path” formalisms for tracking air flow and calculating aerosol deposition in the lung. The single-path method calculates deposition in a typical path per airway generation similar to the ICRP, while the multi-path method calculates particle deposition in all airways of the lung to provide regional-, lobar-, and airway-specific estimates (CIIT Centers for Health Research, 2005).

A panelist suggested that data for interspecies comparisons of clearance based on allometry might inform age-dependent differences in clearance; however, some panel members were skeptical of using this approach for intra-species comparisons. They said the basis for allometric scaling equations in the RfC methods are interspecies differences in intermediate metabolism, not weight differences of individuals within a species. Additional data for evaluating age-specific differences in particle clearance may be found

in the reports by Snipes et al. (1997), Bailey et al. (2003a), and in the ICRP model (ICRP66, 1994). While there are a few references that evaluated the clearance issue in the nose, the data are too limited for use in adjusting dosimetry (Asgharian et al., 2004).

Two panel members noted that childhood asthma, which is common, may influence tracheobronchial clearance, but data are lacking to quantify this. Since the lung itself is a target organ, cumulative effects on the lung can result in changes in deposition and clearance rates over time due to changes in airway architecture and physiology. If the site of deposition and clearance is also the target tissue, it may raise key issues in estimating dose rate changes.

5.2.2 Considerations in Using Time-Weighted Averaging

The panel was asked to comment on the use of a time-weighted average (TWA) approach for calculating deposited dose differences across various age periods in the absence of direct data on retained doses. One panel member commented that using the TWA of the deposited dose does not account for clearance differences across age. Another member thought that including the TWA approach as a way to develop ratios is acceptable, but this approach really does not need to be provided because users can develop their own TWA as needed for the time periods of interest to them. Other panelists recommended showing cross-sectional deposition ratios (e.g., for 10 year olds) because that would be informative as a bounding exercise, but they said including the TWA approach as a concept is a distraction. Two panel members recommended removing Figure 6 (which shows the ratio of the TWA deposited dose for a 10 year old versus the deposited dose for an adult) from the document. They cautioned against presenting any specific time window, in order to ensure that readers do not give specific toxicological significance to the example shown (e.g., a reader may infer from the document that the 10 year time-frame TWA data from Figure 6 is important for all situations). However, they suggested adding a discussion about addressing the life-stages of interest when evaluating child versus adult dosimetry. Another panel member said that including specific TWA calculations might not be necessary, but the document should discuss the TWA issue so users would know how to apply averaging over relevant age periods for various endpoints.

Another panelist thought TWA usage was an exposure assessment issue, but the document tried to use it to calculate a dose deposition rate. He said two important considerations in TWA usage are the periods of interest for comparison and the selection of the dose metric. The document needs to go more deeply into the implications of these two considerations. The document also needs to further discuss the conclusions reached from using the TWA approach and to add caveats describing the limitations of the conclusions.

Panelists said the document was unclear whether short-term averages over small increments in the life of a child could be compared to the adult average. One panelist also noted that the basis for the endpoints impacts the correct averaging approach. For example, there are dramatic differences if one assumes the same exposure scenario

between rats and humans versus making the assumption of a 24-hour continuous exposure (see Figures 6a and 6b in Jarabek et al., 2005). The use of a TWA concept comes into play in the lifetime average daily dose (LADD) calculation for chronic exposure. The key consideration is how to evaluate risk over a lifetime based on age-specific kinetics. This can be difficult if a cross-sectional averaging approach is used, since early doses may be retained and may be the driver for effects. These issues are similar to those noted in EPA's Guidelines for Carcinogen Risk Assessment (US EPA, 2005).

Another key question is how to adjust for sequential periods of susceptibility using a series of cross-sectional evaluations. The TWA of the deposited dose would not address this. For example, if the period of interest is for a 3-month old and children's (or adults') pulmonary clearance is 90 days, then the 3-month old would not reach steady state in the life-stage of interest. Therefore, comparisons of child-to-adult deposited dose may be problematic. An alternative is to use biologically-based dose response models that could sequentially adjust the clearance calculation based on the retained dose achieved in the previous life stage (Jarabek et al., 2005).

Responding to concerns about the age cutoffs assumed in the document's TWA calculation, the authors explained that their rationale for the age cutoff of 10 years for the comparisons was based on empirical data showing that ventilation rates and surface areas are similar to adult values by this age. One panelist noted that in relating this to lifetime risk, chronic is usually defined as 7 years in a human, and the 10-year range is approximately equal to chronic consideration. However, another said that consideration of surface area and ventilation rate for only 10 years does not adequately address changes in the respiratory tract, because respiratory tract architecture changes significantly with age up to 21 years. It was recommended that the parameters and age periods defined in the ICRP66 model (ICRP, 1994), notably that the respiratory tract is considered "adult" at 21 years, might be better values to use as the basis for the analysis.

5.2.3 Consistency with RfC Approach and Use of Alternative Models

In clarifying whether the approach used in this document is consistent with RfC methods, one panelist observed that the RfC methods incorporate dose-response analysis on the basis of the duration-adjusted HEC. The HEC is an exposure estimate that is derived based on ratios of internal dose metrics. The framework document develops ratios of internal dose (deposited dose) for assessing potential UFs. Another member clarified that the RfC process occurs in sequence -- first the dosimetry adjustment is made, then the selection of the magnitude for the intra-human UF and interspecies UF.

The panel advised that including updated and more sophisticated models would be consistent with the RfC guidance and should be considered by the authors. The document should encourage users to start with the best model, then simplify as required by the available data set. The principle of using this hierarchical approach should be better reflected in the document and a table from Chapter 3 of the RfC methods that articulates the hierarchy was provided. Additionally, the authors should use more recent

models such as the ICRP or MPPD models to evaluate age-specific dosimetry. Using these models would be advantageous since the RfC dosimetry model was limited by the need to empirically fit a dataset available across species (Raabe et al., 1988). These newer models for the human and rat are more mechanistic and address a wider range of particle diameters. These models also can provide information regarding the variability of some parameters. A recent paper by Bolch et al. (2001), on the variability of ICRP model parameters was noted as an example. Two members suggested the document include a more detailed discussion of the basis for model and parameter selection, particularly in light of its reliance on the work of Stanek et al. (2004) for data on age-specific ventilation parameters (because the Stanek report was only an abstract). The panel recommended that experts in respiratory physiology and inhalation toxicology be consulted regarding age-specific physiological parameters such as ventilation rate or to use established references for these parameters such as the ICRP values.

5.2.4 Additional Consideration of Dose Metrics and Extrarespiratory Effects

The panel also discussed the approach used for considering extrarespiratory (i.e., systemic or remote to the respiratory tract) effects of particles and suggested several key points for the authors to consider. One member suggested normalizing the data on a lung weight basis because this would account for dosimetry differences resulting from age-related changes in the amount of the dose reaching pulmonary absorption sites. Another panel member added that if body weight is used for normalization, consideration should be given to using only the dose that penetrated to the pulmonary region, as this is likely the dose available for uptake. (Unless the particle is highly soluble, deposition in the upper two regions will be cleared and is typically not available for absorption). For extrarespiratory dosimetry, particle solubility is a key consideration to include in the framework. The uptake of substances may change with age because of different blood solubilities resulting from differences in blood protein and lipid content. It might be useful to think of extrarespiratory effects based on two subcategories of particles: 1) soluble particles having age-related differences in dosimetry resulting from differences in their blood uptake, and 2) insoluble particles which have slower clearance, but which are taken up in the pulmonary region by mechanical means.

A panelist noted that the analysis of effects of particles must consider whether the *size* of the particles, number, or the *total mass* of the particles is more relevant to causing toxicity. Careful characterization of the activity diameter to define the relevant dose expression would also be useful (U.S. EPA, 1994; Jarabek et al., 2005). The activity diameter expression takes into account the "activity" of the physical property of the particle. For example, if the toxicant is distributed only on the surface, then the activity median diameter is equal to the surface median diameter (U.S. EPA, 1994). Further discussion of issues related to activity diameters can be found elsewhere (Hofmann and Koblinger, 1989). The panelist also referred the authors to a recent approach using the MPPD model for ambient particulate (PM_{10}) (U.S EPA, 2004; Brown et al., 2005).

Another panel member noted that extrarespiratory dosimetry needs to consider particle diameter to account for ingestion of particles following mucociliary clearance from the

tracheobronchial region and nasopharynx. As a simplifying assumption, one could consider systemic dosing for all of the particles deposited in the lung, although not all of the particles that are cleared to the GI tract become systemically available. Other routes of lung clearance such as lymphatic drainage also may be important. All the clearance routes should be discussed in the document.

5.2.5 Configuration of the Framework for Particles

The panel discussed the overall configuration of the framework for particles (Figure 11a in the sponsor's document). Some members thought the overall flow and grouping were presented clearly in the submission, while others said that working through the flow chart was not intuitive and could be improved. To aid the reader of this report, the original framework (Figure 1a.) and the framework as ultimately suggested following various changes and iterations from the panel (Figure 1b.) are shown in this meeting summary.

The Chairperson asked whether duration of exposure is a reasonable entry point for the framework flow chart. A document author explained that many acute exposure guidelines do not explicitly consider children versus adult kinetics; therefore, this framework started with duration of exposure as an entry point in order to highlight acute versus longer-term exposure scenarios. Panel members gave several suggestions on this point. Some said that starting the flow chart with a question of exposure duration may give the incorrect impression that this consideration relates directly to UF selection. Alternative suggestions for beginning the flow chart included mode of action (MOA), target region, or particle size. It was noted that although the detailed MOA is unknown for many chemicals, all that is needed for this framework is information on the nature of the effect. One panelist suggested using the *type* of agent as a starting point for the flow chart; others responded that the document already had addressed this in part by having separate frameworks for particles and gases. Other members suggested starting with particle size, then branching to solubility, and then age group. If the authors continue to use duration of exposure as the entry point, they should clarify what duration is to be considered – is it duration of exposure to the child, duration of critical windows of vulnerability, or duration differences in adults compared to children? Based on these discussions, a revised framework starting with consideration of mode of action or nature of effect was suggested.

The panel also commented on the arrangement of the longer-term branch in the framework figure (Figure 1a). Two panelists suggested arranging this branch in the same way as the shorter-term branch and clarifying the intent of the "retained dose" box. Also, the framework needs to clarify why the retained dose is not considered in the acute branch of the proposed flow chart. An author commented that the deposited dose would be sufficient for acute exposures, while longer-term exposures would need to consider the retained dose, even though data to develop retained dose as a default approach might be lacking. Retained dose was included in the framework since it would be the preferred dose metric for longer-term concerns (particularly for relatively insoluble particles where long residence time in the lung and resulting chronic pathogenesis may be of greatest concern). The issues related to differences in assumptions regarding retained dose for

particles of differing solubility were incorporated by the panel into the revised framework (Figure 1b). Using deposited dose as a default would be consistent with RfC methods, and the panel agreed that when the retained dose could not be determined, the deposited dose could serve as the default.

The panel also discussed the "acute pathogenesis" arrow in the flow chart and suggested that the decision point to move from the longer-term to the acute side of the framework should include temporal windows of vulnerability. The term "temporal windows of vulnerability" was considered more appropriate to use than the term "acute pathogenesis". This concept could be applied in the framework by identifying the temporal window of vulnerability and calculating cross-sectional dose metrics (deposited dose rate) for the time window. Panelists noted there might be significant variability within a window of vulnerability, such as the timing and the extent of synapse formation in postnatal life (i.e., it would be much different from birth to year one versus from years 9 to 10). An author asked the panel if deposited dose is a relevant metric for short exposures, such as 15 minutes. A panel member replied that although many chemicals do not act in accordance with Haber's law, calculating the ratios of deposited dose could still be useful if the same saturation level occurs across age groups. Age-dependent differences in uptake fraction also need to be considered. In addition, the framework does not address the role of retained dose in acute effects.

Panel members offered numerous other specific comments on the framework for particulates. The box "target region of RT" should be renamed "target region", since extra-respiratory effects may also be of concern. This box was ultimately renamed to deposited dose in the final figure developed by the panel (figure 1b). The ICRP model divides the respiratory tract into subregions, and the authors might do this also. Alternatively, it might be more informative for the authors to reorganize the framework chart by age, rather than by region of the respiratory tract. This would allow the user to more easily identify the regions of interest for various exposed populations and would present the figure in a way that is most easily interpreted by a risk assessor. In discussing the layout of the flowchart branches, several panel members noted that ideally one should be able to sort the calculated dose ratios in a variety of ways. (This is reflected in Figure 1b as a note under the target regions for adding a matrix of ratios by particle diameter and age). Sorting by multiple variables could be done using a matrix that shows the ratio categories by age group, target region, and particle size. Use of a matrix also would help identify areas of missing data.

The panel thought that identifying groups in the framework as "of concern" or "not of concern" as shown in the original Figure (1a) was not appropriate because, without analysis of human variability and knowledge of retained dose, the proposed ratios only provide information on deposited dose, not on "concern" or risk. Categorization of a ratio value of less than 2 as group 3 (see Figure 1a) was questioned because of the lack of data on individual variability. Panel members raised concerns about the specific groupings and the basis for selecting specific ratio values to use as cut points for defining these groupings. The panel recommended that these values not be given too much weight. Rather, the groupings should be characterized as dosimetry adjustments and not

as identifiers of groups of concern. In addition, it was suggested that the underlying analysis that led to the selection of cut points needed greater discussion if the identification of specific groups were to be retained.

The panel discussion on the particulate framework (Figure 1a) led to suggested changes as shown as the "Revised Framework for Particles – Figure 1b" in Section 7 of this report.

5.3 Discussion of Framework for Gases and Vapors (Charge Questions 7 to 11)

5.3.1 General Issues

The sponsor's document presents analyses for evaluating age-related differences in respiratory tract dose (for Category 1 gases and respiratory tract effects of Category 2 gases). The document also presents analyses for evaluating age-related differences in extrarespiratory dose (for Category 3 gases and systemic effects of Category 2 gases). An observer at the meeting commented that it would be useful for the document to offer guidance for determining whether a gas is best described as Category 1 or 3. Such guidance might include a table of attributes of each gas category. It was noted that such guidance is available in Chapter 3 of the 1994 RfC methods (EPA, 1994). The review by Hanna et al. (2001) also discusses the categorization scheme.

In response to a comment regarding the document's failure to include Category 2 gases, a panelist commented that EPA has corrected the dosimetry of Category 2 gases and that this has previously been made available. The panelist noted that the Category 2 gas equations include parameters for both Category 1 (e.g., ventilation rate, surface area) and 3 gases (e.g., partition coefficient). Category 1 and 3 equations represent limiting cases that were derived from the more comprehensive Category 2 equation based on simplifying assumptions. For this reason, using the Category 2 equation would always be the optimum approach, but it is appropriate to use the Category 1 and Category 3 cases if more details are not available, as long as the simplifying assumptions are documented. As an example of Category 2 dosimetry calculations, a panel member noted that they had compared a series of mass transfer coefficients, which included that for a Category 2 gas such as ozone (Ginsberg, 2005). Hanna et al. (2001) presents discussion of the gas-phase mass transfer (k_g) and liquid-phase mass transfer (k_l) terms of the overall mass transfer coefficient (K_g) as a way to distinguish Category 2 gases from Categories 1 and 3.

Several panel members thought the document should encourage using the most robust approach, using simplifying defaults only when required. Presentation of equations (i.e., for Category 3 gases on page 31 of the sponsor's document) should start from the most complex form, and then describe how the variables cancel out when simplifying assumptions are made. For example, panel members pointed out that the term for describing ventilation rate over cardiac output (V_E/QC) was not included in the equations -- probably because the authors had assumed VE/QC had the default value of "1". They said there are cases where this term is not "1," so the document needs to identify and describe the simplifying assumption that was made. Regarding this series of equations, another panel member noted that it was unclear whether the equations on page 31

referred to *hepatic* clearance or to *intrinsic* clearance. Another example of a simplifying assumption used in the analyses presented in the sponsor's document was made for Category 1 gases by leaving out the term containing the mass transfer coefficient (K_g). This reduced form for the default essentially assumes that the K_g is large (so that the exponential term goes to zero) or that the K_g had the same value for adults and children. It is not clear that the K_g parameter is age-independent, and this parameter should not be dropped out of the equation.

5.3.2 Issues Related to Portal of Entry Effects and Acute Exposure

A panel member noted one important issue that has been developed to extend the RfC methodology is the use of tissue concentration in localized epithelia (e.g., respiratory versus olfactory) versus flux to describe the dose metric for nasal effects of Category 1 gases (Bogdanffy et al., 1999; Andersen and Jarabek, 2001; Andersen and Sarangapani, 2001). It was suggested that the portal-of-entry side of the flowchart for Category 1 gases (and direct respiratory effects of Category 2 gases) should present this distinction. Based on work of Andersen and Sarangapani (2001), one can derive tissue concentrations and develop bounding estimates for Category 1 gases. Other panel members agreed that this consideration should be presented in the document. Based on this suggestion the panel modified the framework for gases to include this distinction for portal of entry effects (compare Figure 2a versus Figure 2b).

Several considerations impacted by the duration of exposure (acute versus longer-term) were discussed. One member suggested that the framework for gases should be divided by acute and chronic exposures as was done for particles and the panel modified the framework per this suggestion. Some panel members questioned whether a steady state consideration is needed -- or is even applicable -- to acute exposures. Some panelists thought chemical-specific data might be required to answer this question, but they said that in many cases the uptake phase begins 15 to 30 minutes after the start of exposure and steady state begins to be reached within one hour. A limiting case for non-steady state conditions was proposed as the product of ventilation multiplied by concentration and normalized to body weight, assuming absorption from the lung is unchanged. This approach would allow development of calculations for comparing adults and children that do not rely on steady state assumptions. Another suggestion was to use the fat:blood to blood:air matrix from the RfC guidance document (as above) to develop information on the amount of time required to reach steady state. Based on these discussions for acute exposures, a panelist suggested that the document (and flowchart) start by identifying duration of exposure, then use examples to highlight how dose differs by age, and then discuss methods for conducting a more detailed evaluation of the chemical of interest. The framework was modified to separate chemicals by mode of action or nature of effect, then by duration category, and then with alternative dose metrics based on whether steady-state conditions apply. The suggestions regarding alternative dose metrics were also added to the revised framework (Figure 2b). It was noted that some of these issues may already have been addressed by the Acute Exposure Guideline levels (AEGL) committee.

The panel also discussed whether parent compound should be considered more than metabolites in acute exposure situations. While metabolites can be relevant for acute exposures (parathion was noted as an example) most panelists concluded that for acute exposures where the metabolite was the active form, chemical-specific data or a PBPK model should be used to assess age-dependent kinetics. Another consideration addressed by the panel was whether the framework should account for both maximum tissue concentration (C_{max}) and area under the curve (AUC) as dose metrics for acute and longer-term exposures. It was noted that separate considerations impacting human variability may apply to C_{max} and AUC, since C_{max} may be more susceptible to extreme fluctuations in breathing rate. In addition, C_{max} is a dilution function and scales to body weight while AUC scales to body weight to the 0.75 power. The framework for gases was modified by the panel to address these various considerations (Figure 2b).

5.3.3 Issues related to Evaluation of Systemic Effects

The panel provided a number of comments regarding the analyses in the authors' submission on age-related differences in extrarespiratory dose (i.e., for systemic effects of Category 2 gases and for Category 3 gases). These included assumptions about steady-state conditions, sources of data on partition coefficients, and impacts of assumptions about blood flow and metabolism. Comments from the panel on these issues are provided below.

A panelist commented that it was generally appropriate to use the RfC process with reliance on partition coefficient ratios and steady state equations; however, the authors should consider the work of Andersen (1981) for steady state equations. The panel discussed how steady state applies to HEC calculations and how the RfC approach assumes steady state is achieved to extrapolate from the laboratory animal to the adult human. A panel member noted that the HEC adjustment is not intended to be inclusive of the consideration of child versus adult kinetic differences. Rather, if one has human equivalent concentrations in adults (based on animal data) then one still needs to consider another factor to get the equivalent concentration in a child. It was further noted that using the framework for acute values raises a concern since it is unlikely that a child will have reached steady state. Panel members recommended providing an analysis using two limiting cases: (1) for long-term exposure use steady state equations, and (2) for short-term or acute exposures use ratios based on chemical uptake (these suggestions are included in the structure of revised framework for gases (Figure 2b). A matrix similar to the one in Chapter 4 of the RfC methods (EPA, 1994), based on the blood:air versus fat:blood partition coefficients for different durations of exposures could be useful for this determination.

Several comments were made regarding the analysis of partition coefficients. Substantial differences in partition coefficients for children and adults have been reported in the literature, and these differences did not seem to be reflected in the current document. The authors need to evaluate the basis for these differences.

The document should add more discussion of deviations of calculated versus empirical partition coefficients and the implications for the analysis. A panel member commented in post meeting clarification that the issue to be captured here is reliability of partition coefficient estimates based on structure-activity relationship, *in vitro* measurement, or gas uptake approaches and their relationship one to the other. This panelist recommended the authors cite key references in this area of work. One panelist said there is no single value for the blood:tissue partition coefficient because it varies with lipid content, and lipid content varies with meals. Another panelist noted that Lerman et al. (1984) reported a correlation between partition coefficients and both blood lipid content and age for two-carbon halogenated compounds. Also, if the authors revise their document, they should confirm that the blood:air partition coefficients listed in Table 3 of their submitted document are correct because they differ from values calculated by other investigators. Another member thought the estimates in Table 3 of the sponsor's document may underestimate the difference in age-dependent blood:air partition coefficients.

The panel discussed the bounding analysis in Figure 9 of the sponsor's document, which presents ratios of child:adult steady-state blood concentrations for a range of blood:air partition coefficients. One panelist noted that the analysis assumes adult metabolism results in 100% extraction, while in very young children hepatic extraction can be very low. Panelists advised caution in making inferences regarding age-related differences in metabolic parameters. Although intrinsic affinity is a function of the enzyme itself and will not change with age (for a given isoform), apparent affinity can change based on the measurement environment. Apparent age-related differences in metabolism may reflect measurements made in circulatory blood versus in liver tissue. Similar issues must be considered when extrapolating K_m or V_{max} data from *in vitro* studies to *in vivo* applications. Panel members recommended adding information on the time course of age-dependent enzyme expression for key metabolic systems. This information would help to put the bounding scenarios (such as Figure 9 of the sponsor's document) in correct perspective. Figure 9 of the submission shows an intercept at a value of 1, suggesting that the child steady state blood concentrations can never be lower than those of adult. The document should clarify that this result is based on the simplifying assumptions that were used. It may be useful to use studies by Clewell et al. (2004) and Poulin and Krishnan (1999) to give estimates between the extremes used in the current document. It also was noted that the analysis presented in Figure 9 considers only liver extraction and not pulmonary clearance, which is why the ratio of child:adult steady state blood concentrations presented in Figure 9 are a maximum estimate.

Several panelists commented that Figure 9 does not consider age-dependent differences in blood flow**.** Because blood flow limitation is a critical consideration, they thought the document should be clear how blood flow can impact the analysis. They recommended that the document include examples of blood flow-limited metabolism in an adult and in a child as bounding cases. The need to discuss the implications of blood flow to the liver was also noted, since blood flow limitation could quench age differences in metabolic rate (i.e., maximal tissue metabolism: V_{max}). Chemicals that are flow limited in adults may not be flow-limited in children due to differences in intrinsic clearance. Several panelists also made suggestions regarding Figure 10 in the document. It was not clear if

the analysis represents the high or low extraction case. Additional analyses were recommended to develop bounding estimates for the analyses shown in Figure 9 and Figure 10. These recommendations included the following: 1) for parent compounds add a comparison for flow-limited metabolism in both adult and child to Figure 9, 2) for reactive metabolites add a figure similar to Figure 9 for rate of metabolite produced divided by volume of the liver, assuming flow-limited metabolism in both adult and child, 3) add a figure similar to Figure 10, but for the child/adult ratio of the steady state rate of metabolism divided by volume of the liver; and 4) for stable metabolites create plots similar to Figure 10, showing child/adult ratios for stable metabolite steady state concentrations (this could be done using isopropanol/acetone results from the life-stage model in Clewell et al. 2004).

The impact of extrahepatic metabolism on uptake of category 2 and 3 gases was also discussed. Panelists suggested the document clarify that the analysis is limited to enzyme systems in the liver and would not necessarily apply to metabolism in other tissues (e.g., chemicals metabolized in the blood by esterases, or chemicals that exhibit whole-body clearance). They thought the document should discuss extrahepatic as well as hepatic metabolism and should clarify the types of chemicals to which the current analysis can be applied. For example, the analysis in Figure 9 is limited to chemicals that are metabolized by enzyme systems that exist primarily in the liver (e.g., the CYP2E family). Another panelist noted that extrahepatic metabolism may be more of an issue for chemicals that are slowly-metabolized, and this consideration should be given as a caveat in interpreting the data.

Another panel member identified the need to consider the dose-dependence of various metrics, noting that for some chemicals blood flow may be the limiting parameter at low doses while V_{max} may be limiting at high doses. Therefore, the dose is an important factor to consider when identifying the metric for calculating ratios for children versus adults. Furthermore, any evidence for potential affinity differences in blood partitioning and enzyme kinetics resulting from of differences in age should be discussed.

The panel recommended adding more citations of the original published data that serve as the bases for the analyses. Presenting more of the original data might encourage the collection of further data, and thus reduce uncertainty and help move away from default assumptions. One member said that an example of data that could be readily collected would be blood:air partition coefficients. It was also suggested that the authors consider compiling a resource appendix of what has been published in this area. As suggested above in the discussion of particulates, engaging relevant experts to evaluate sources of data used in analyses also could be helpful in selecting appropriate data sets. For example, soliciting expert opinion regarding the evaluation of which enzyme data sets to use for further analyses was recommended.

A panelist recommended clarification of the basis for the data in Table 4 showing glomerular filtration rate (GFR) changes with age. The units must be presented in this table because the child value (expressed as a fraction of the adult value) is different for the GFR expressed in units of mL/min than when normalized data are expressed as a

fraction of total blood volume (since blood volume changes with body weight). These data need to be combined with blood flow information before they can be used to predict differences in GFR between adults and children.

The panel also discussed using the framework for a toxic metabolite. One panelist said inclusion of reactive metabolites is feasible using bounding estimates based on maximum extraction by metabolism and on flow-limited metabolism in both adult and child (as shown in Figure 2b). This approach could be demonstrated using the life-span model developed for isopropanol/acetone (Clewell et al., 2004). Another relevant source of data could be a recent analysis that divided Category 3 gases into sub-types based upon partition coefficient and hepatic extraction rate relative to blood flow, in order to characterize how chemical-specific properties can affect dosimetry (Ginsberg et al., 2005). Other work with Category 3 gases provides a framework for evaluating the variability in systemic dosimetry among age-groups (Pelekis et al., 2003). It also would be worth presenting the work done with kinetic models to estimate variability in reactions and metabolites. Sources recommended for such analyses included the following: O'Flaherty (1989), Fiserova-Bergerova et al. (1980), Fiserova-Bergerova (1983), Droz (1985), Ultman (1994), Price et al. (2003) and the NRC (1986) *Drinking Water and Health Volume 6.*

Although several references that provide approaches for including metabolites in the framework were suggested, the panel also had some cautions. For example, the use of data on "active" metabolites needs to consider whether the biological activity reflects differences in enzyme activity, as well as differences caused by loss from passive processes, such as reaction with water. Therefore, to assess age-dependent differences, one would need to determine the rate of active metabolite loss empirically and not rely on the rate predicted by enzyme kinetics. Another difficult issue is how to define "reactive" versus "stable" metabolites. The revised framework added this consideration (Figure 2b), with some pertinent issues noted here. One member defined "reactive" metabolites as those metabolites that are retained in the tissue where they are formed. Another noted that "stable" metabolites are discussed in Volume 6 of *Drinking Water and Health*, adding that a default approach for addressing the kinetics of stable metabolites might be that stable metabolites have kinetic profiles similar to the parent. Dahl et al. (1991) also presented a thermodynamic definition of reactivity. The kinetics of isopropanol/acetone was noted as a potential useful case study to explore. One panelist questioned whether a general default approach to reactive and stable metabolites could be developed, since metabolite formation depends on rate of metabolism and age-specific data on enzyme kinetics would be needed (as suggested by the need to use Chemical-specific data or bounding estimates as shown in Figure 2b). Others commented that stable metabolites can be more difficult to consider than reactive metabolites, because it is more difficult to identify the limiting processes in their kinetic profile. Also, the document would need to add text on age-related changes in the clearance of the metabolite.

Panel members commented on other specific points of the flowchart for gases and vapors. They said the flowchart does not need a box labeled "validated PBPK model?" since the user has already answered this question before starting down the flow chart. One panelist

suggested two different flowcharts: one for Category 1 gases and another for Category 3 gases. Others did not agree because any default description, regardless of gas category, can be extended to express the dose metric as a tissue concentration when sufficient data exist on the mode of action. For the box in the draft framework (Figure 2a) labeled "Clearance via metabolism?" the panel said the appropriate metrics would be clearance parameters, such as rate constants for elimination. It was noted that the flowchart does not indicate if the tissue dose is blood flow limited; however, this would not be known unless the K_m and age-dependent V_{max} were known, as well as the blood flow to the organ.

The panel discussion on the gases and vapors framework (Figure 11b in the document) led to suggested changes as shown as the "Revised Framework for Particles – Figure 2b" in Section 7 of this report and as noted in the text above.

5.4 Other Considerations (Charge Questions 11 and 12)

The panel discussed whether a similar framework should be developed for oral exposures or whether oral exposures should be incorporated into one of the current frameworks. In general, panel members thought that a similar analysis for oral exposures would be of value and is feasible (as demonstrated by previous work on a parallel approach across routes – see Jarabek, 2000 and Rigas et al., 2000), but that it should be done as a different framework in a separate document. They advised preparing a specific oral document, because consideration of ingestion requires additional specific parameters such as GI uptake. Panelists noted the oral route may have some simplifying cases, such as nonvolatile compounds that form reactive metabolites for which the dose metric is AUC in the liver and absorption scales across age. A more difficult case would be a chemical having interplay between metabolism and ventilation.

One member discussed validation of the proposed framework, saying validation is often seen as the ultimate blessing, but it does not equate to scientific truth. Rather, validation is part of the scientific process comparing prediction versus observation. The underlying empirical data, the models, or both can contain errors. The real value of validation comes in identifying and then considering the sources of discrepancy.

Several approaches for evaluating and testing the sponsor's framework were discussed. Most panelists agreed that comparing the framework results and their supporting analyses to the analyses of others would serve as a reality check and would provide an opportunity to investigate the sources of any discovered differences.

The panel recommended comparing the model results used in the document to results from other existing models such as the ICRP model, MPPD models, and also to the analyses of others (e.g., Martonen et al., 2000). Increased simulation of existing models was recommended as a source for further information. For example, sensitivity analyses should be conducted by varying key model parameters to examine the potential uncertainty in the predicted dosimetric differences between adults and children. Markov Chain Monte-Carlo (MCMC) methods can be employed to run the models developed in

adults and to vary the parameters to make inferences on relative differences between adults and children. This approach is useful to evaluate human variability. Chemicals with existing models should be used as examples because they can inform relationships to use for compounds where data are insufficient.

The panel recommended using existing data sets to characterize variability whenever possible. One recommendation was to use pharmaceutical chemicals with data on both children and adults. Subsets of the available data could be selected based on analogy or critical attributes (e.g., lipophilicity, functional groups, etc.) to make the data more representative of the chemical being considered. However, extrapolating data from pharmaceuticals to other chemicals (e.g., environmental pollutants) may not be justified if different enzyme systems are involved. Additionally, extrapolating drug data might not be appropriate if the administered doses were substantially higher than the doses from the chemical being considered (often environmental concentrations). Nevertheless, the panel acknowledged that drugs are routinely used to understand enzyme kinetics. Existing analyses such as the work of Bolch et al. (2001) also can provide data on variability for parameters of interest.

The panel members identified high priority data gaps regarding age-dependent differences in toxicokinetics. They noted several uncertainties in understanding adult-to-child differences that were not addressed in the framework. These uncertainties included the following: (1) the effects of disease states in children (cystic fibrosis, asthma); (2) age-related differences in clearance; (3) physiological switch points to oronasal breathing; and (4) impacts of differences in activity patterns. Recommended areas for further research included (1) age-dependence of blood:air partition coefficients; (2) liver blood flow by age; (3) the impact of mutation frequencies by age; (4) biological understanding of the mechanisms by which the body sets and recognizes checkpoints with aging; (5) enhanced understanding of age-dependent changes in enzyme activities; (6) characterization of extrahepatic metabolism; (7) developmental architecture and airway size (including the nasal cavity) developmental patterns; and (8) increased ability to use microscale studies of metabolism.

6. Observer Technical Comments

A meeting observer commented that EPA is updating the RfC methods and that it would be useful to compare the sponsor's work with the updated RfC effort.

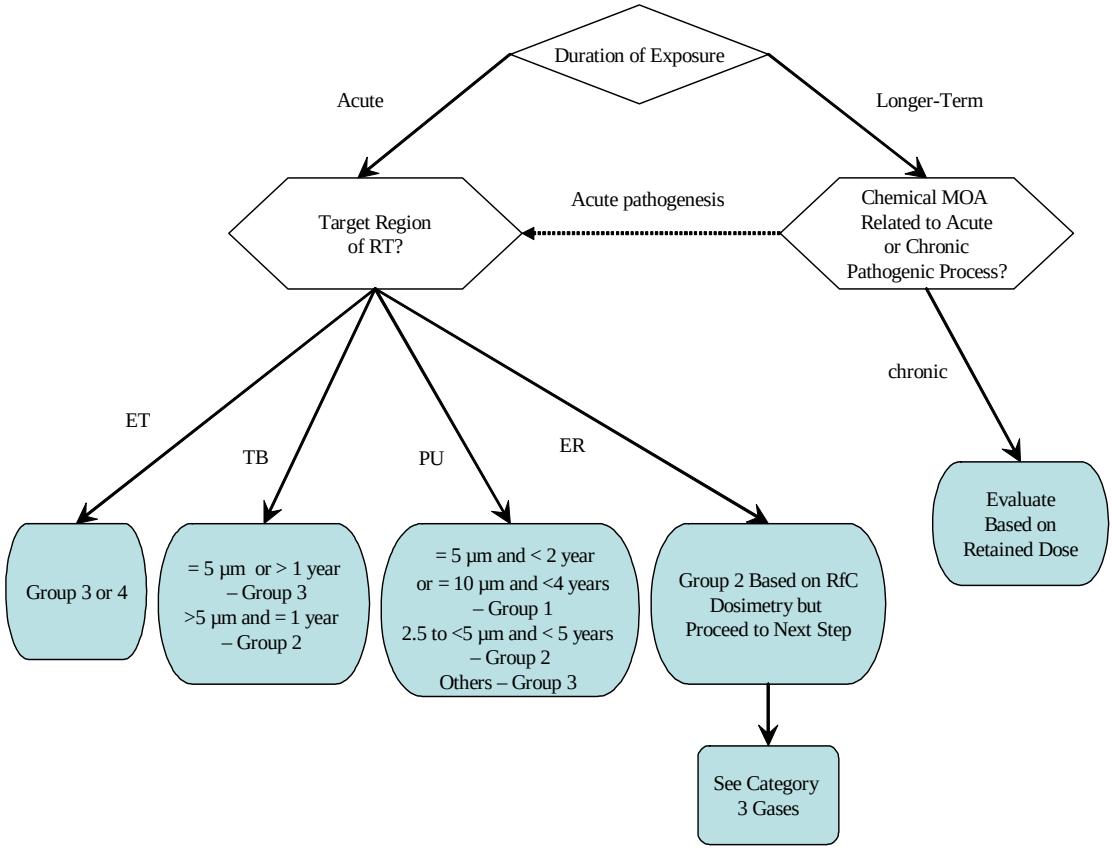
Another observer commented that it would be useful for the document to include guidance in determining whether a gas is Category 1 or 3. A panel member replied that such guidance appears in the current RfC methods (Chapter 3) and other publications (e.g., Jarabek, 1995; Hanna et al. 2001), and this information could be added to the sponsor's document.

A third observer commented that refinements to the framework would be most useful if a case study were added.

7. Revised Frameworks

Framework figures for particles and gases are shown below as submitted by the authors for input by the expert panel (figure 1a and 2a) and the revised frameworks drafted by the panel during the meeting (figures 1b and 2b).

Conceptual Framework – Particles



Group 1 = Of concern. A factor of 3.2 does not appear to be sufficient.
Group 2 = Interindividual variability needs to be considered. The estimated ratio falls between 2 and 3.2
Group 3 = Not of concern. The calculated ratio is between 1 and 2.
Group 4 = Children are estimated to receive a lower dose than adults.

Figure 1a. Framework for particles as submitted to the peer consultation.

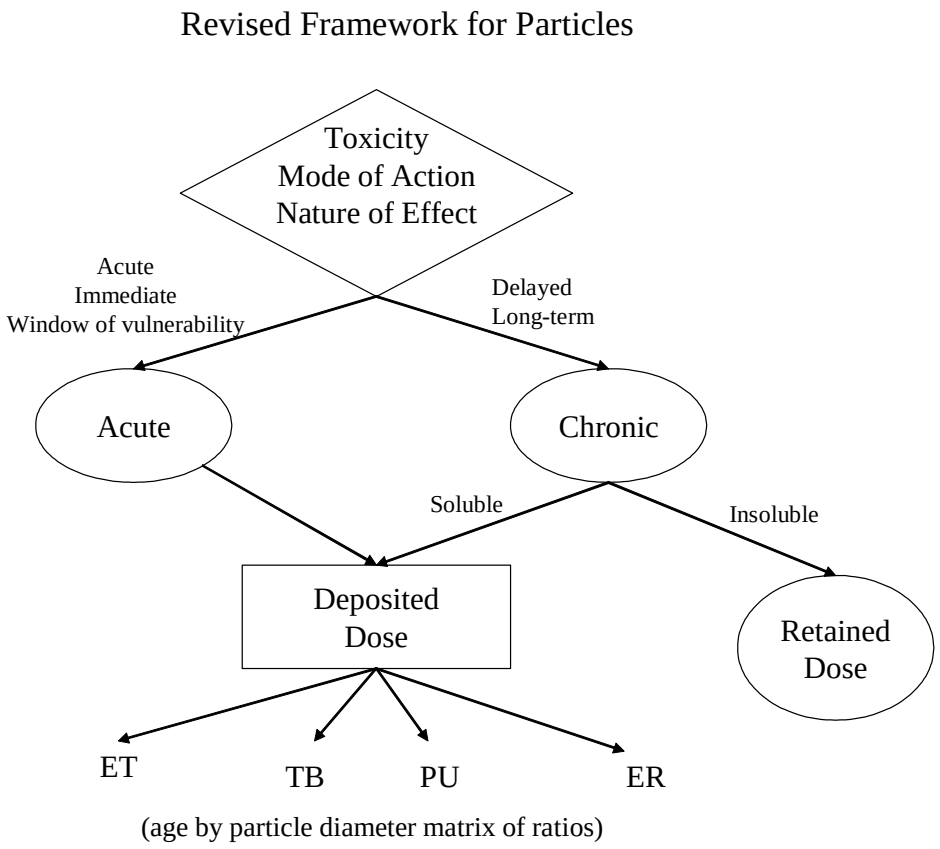
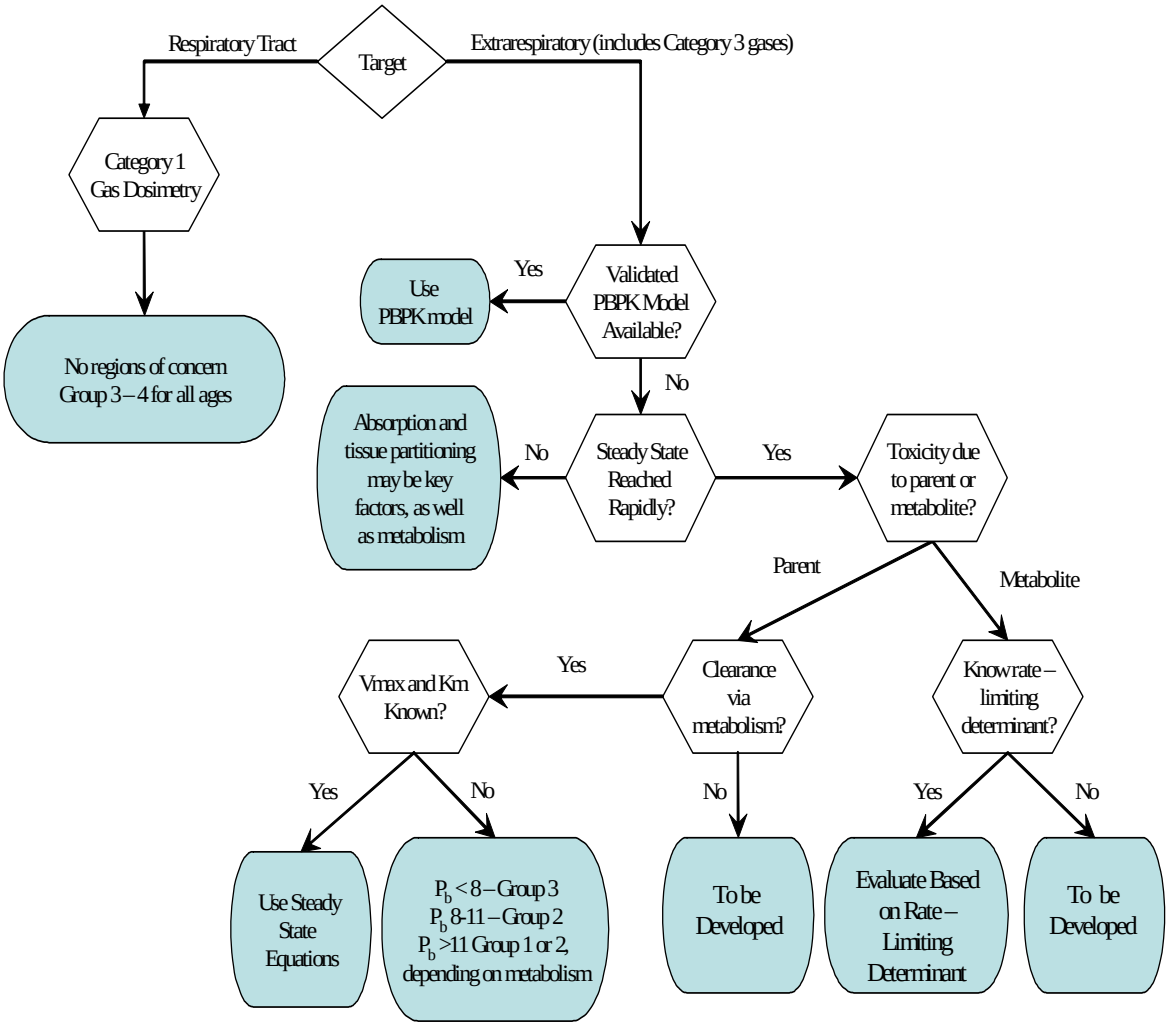


Figure 1b. Revised framework for particles as developed by the peer consultation panel.

Conceptual Framework – Gases



Group 1 = Of concern. A factor of 3.2 does not appear to be sufficient.
Group 2 = Interindividual variability needs to be considered. The estimated ratio falls between 2 and 3.2
Group 3 = Not of concern. The calculated ratio is between 1 and 2.
Group 4 = Children are estimated to receive a lower dose than adults.

Figure 2a. Framework for gases as submitted to the peer consultation.

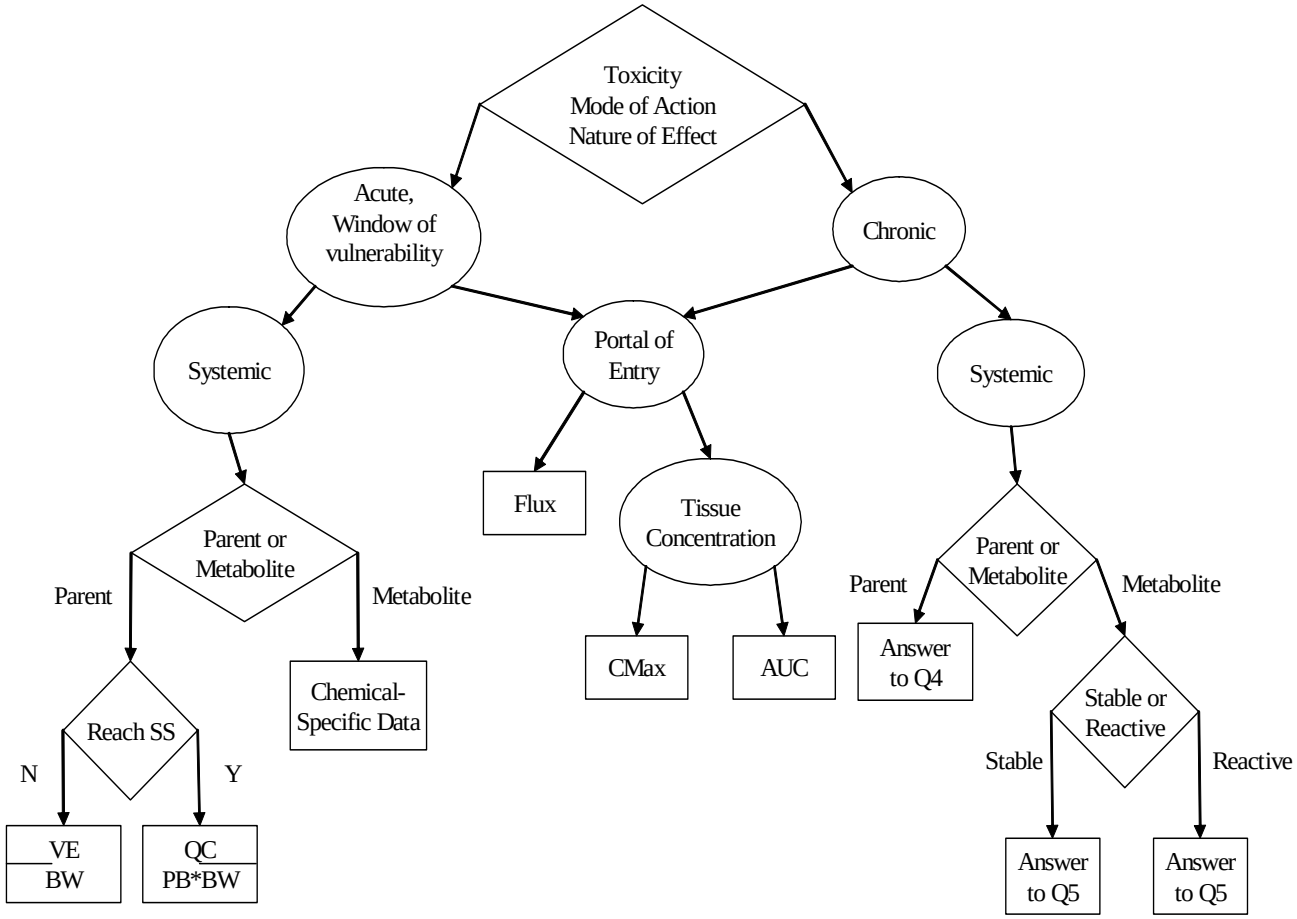


Figure 2b. Revised framework for particles as developed by the peer consultation panel during the meeting.

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APPENDIX A

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APPENDIX B

Peer Consultation on a Draft Framework To Evaluate Whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children

Meeting Materials

March 31, 2005

Kingsgate Conference Center,
Mount Auburn Room
University of Cincinnati
Cincinnati, Ohio

Table of Contents

AGENDA

Peer Consultation on a Draft Framework to Evaluate whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children

Marriott Kingsgate Conference Center at the University of Cincinnati
Mount Auburn Room

Thursday, March 31, 2005

7:30 **Continental Breakfast; Registration and Check In**

8:00 **Meeting Convenes**

Welcome and Logistics: Dr. Dan Briggs, *TERA*

Introductions and Conflict of Interest and Bias Disclosures: Panel Meeting Process, Ms. Annie Jarabek, Chair

8:15 **Presentations on Draft Framework**

Mr. C. Eric Hack, Dr. Lynne Haber, Dr. Jay Zhao, *TERA*

Panel Discussion of Particles (with a mid-morning break)

12:00 **Lunch**

1:00 **Reconvene**

Panel Discussion of Gases (with a mid-afternoon break)

Panel Discussion of Other Charge Items

4:00 **Summary of Discussions and Panel Member Recommendations**

4:15 **Closing Remarks and Evaluation of Meeting**

4:30 **Adjourn**

Overview of the Peer Consultation Process

Introduction

This Toxicokinetics Peer Consultation meeting has been 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).

This panel meeting will discuss a draft framework document intended to evaluate whether the default uncertainty factor for human kinetic variability is adequate for protecting children. The panelists also will provide direction for next steps to refine and expand the framework. The framework the panel will be discussing is not a finished product. It is a preliminary proposal being presented to obtain opinions and guidance from leading experts on how it may be further developed for use in children's risk assessment. The framework and background materials were prepared by scientists from *TERA.* The materials include ideas from several leading researchers in toxicokinetics and physiologically-based pharmacokinetic (PBPK) modeling.

Although this peer consultation is both sponsored and organized by *TERA* personnel, *TERA* used different staff members for sponsoring/authoring the work product (the draft framework document) and for organizing the panel meeting (selecting panelists, developing panel charge). This procedure was followed in order to maintain separation and independence between the work product and the peer consultation panel members who are evaluating it.

The Toxicokinetics Peer Consultation Panel

The Toxicokinetics Peer Consultation Panel consists of eight members. Six of the members are leading experts in toxicokinetics and PBPK modeling. The remaining two members are experts in general risk assessment. Collectively, this panel has many publications and presentations on topics related to toxicokinetics, PBPK modeling, and risk assessment.

Each panel member has disclosed information regarding potential conflicts of interest and biases related to the work product of the peer consultation (the draft framework document) or to the sponsor of the work product (certain *TERA* staff members). *TERA* evaluated these disclosures when selecting panel members. Short biographical sketches and disclosure statements for panel members are provided in this package.

Conduct of the Peer Consultation

TERA developed a "charge" document that identifies 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 and be prepared for the discussions.

The meeting will be organized to make the best use of the time available to hear the opinions of the experts on the charge questions. The meeting will begin with panel introductions and discussion of conflict of interest and bias issues. The discussion will then address the sponsor's draft framework document. The authors of the document will make a short presentation to highlight the salient points and issues and to give the panel the opportunity to ask clarifying questions of the authors.

Public Observation and Comments

Members of the public have been 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.

Meeting Report

TERA will prepare a meeting report summarizing the sponsor presentations, the opinions and recommendations expressed by the panel, and any oral comments from the public. Written public comments will also be included. The meeting report will not be a transcript. The report will be reviewed by the panel for accuracy. Sponsors and observers presenting oral comments will be offered the opportunity to review the summaries of their presentations. The finalized report will then be made available to the public at http://www.tera.org/peer/adultchildtk/actkwelcome.htm .

Panel Charge

Peer Consultation
to Evaluate Adult-to-Child Toxicokinetics Differences

The objective of this Peer Consultation is to discuss a draft framework that proposes methods to evaluate whether the default uncertainty factor for human kinetic variability (HK_{AF}) is adequate for protecting children. While this issue is most definitively addressed using PBPK models, a framework may be useful when a human PBPK model is not available. Panel members are asked to comment on the validity of the framework, its usefulness, and the specific methods and results for relative dosimetry analyses. The panel also is asked to suggest revisions and improvements to this approach.

The following list of questions and issues is to guide the panel discussion of the draft framework. Because this is a peer consultation, the panel will not be asked to form consensus positions on any of the issues discussed. Individual comments and suggestions will be summarized in a meeting report.

Particles

1. Is it appropriate to base the particle dosimetric comparison between adults and children on the RfC approach? What are the potential issues with these calculations, and how might they be improved?

2. To be most appropriate for long-term inhalation of particles, the particle dosimetry analysis should consider the effects of clearance mechanisms on retained lung burden. In the absence of clearance calculations, is it appropriate to use time-weighted average deposition as a dosimeter for longer durations of exposure? Over what time frame can the results of the current particle dosimetry analysis be extrapolated?

3. Is the current approach for calculation of extrarespiratory dosimetry after inhalation exposure to particles appropriate? If not, what approach and what additional parameters are needed to better address the extrarespiratory dosimetry of inhaled particles?

4. The draft framework depicted in *Figure 11a* assumes it is appropriate to make categorical, dosimetric extrapolations from adults to children based upon the properties of the chemical class being considered. Do you agree with this assumption?

5. Does *Figure 11a* make sense and is it useful?

6. *Figure 11a* classifies chemicals into four categories, based on the ratios between estimated dose for children and adults. The ratios defining the boundaries

between the categories were defined arbitrarily. Should Groups 2 and 3 be combined into a category of potential concern since the ratio cut-points are not based on knowledge of variability in children? Do sufficient data exist to derive the boundaries from a quantitative analysis of variability among the different age groups?

Gases

7. Is it appropriate to base the dosimetric comparison of Category 1 and 3 gases between adults and children on the RfC approach? What are the potential issues with these calculations, and how might this approach be improved?

8. Only limited broadly applicable statements are made about the adequacy of the default human kinetic uncertainty factor when a metabolite is the toxic agent. How can the proposed methods for Category 3 gases be extended to estimate the differences in the dose of a reactive intermediate metabolite delivered to adults and children? How can the methods be extended for a stable metabolite?

9. The draft framework depicted in *Figure 11b* assumes it is appropriate to make categorical, dosimetric extrapolations from adults to children based upon the properties of the chemical class being considered. Do you agree with this assumption?

10. Does *Figure 11b* make sense and is it useful?

11. *Figure 11b* classifies chemicals into four categories, based on the ratios between estimated dose for children and adults. The ratios defining the boundaries between the categories were defined arbitrarily. Should Groups 2 and 3 be combined into a category of potential concern since the ratio cut-points are not based on knowledge of variability in children? Do sufficient data exist to derive the boundaries from a quantitative analysis of variability among the different age groups?

Other

12. A comparable framework for the oral route has not been developed. Could it be? Many of the considerations in the extrarespiratory branch of Figure 11b could also apply to the oral route, but additional complications of first-pass metabolism and absorption may need to be considered. What additional age-specific physiological differences and physicochemical properties (e.g., effects of gastric pH and dissociation constants on oral absorption) should be considered to extend the inhalation approach to model oral exposures?

13. Do you have further comments or suggestions for this report or for the framework and the overall approach

Conflict of Interest And Panelist Biographical Sketches and Disclosures

This peer consultation is both sponsored and organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* scientists prepared the meeting materials that are the subject of the peer consultation, while other *TERA* staff organized the consultation. In order to maintain separation and independence between the work product and the review of it, the *TERA* scientists who prepared the meeting materials and framework did not participate in the selection of the panel or the organization of the meeting. *TERA* used funds from an EPA Cooperative Agreement CX-82916801 for this peer consultation.

High-quality, relevant scientific expertise is the most important criterion for selecting panel members. Identification of needed areas of expertise is made through careful evaluation of the draft work product and discussion with the sponsors, authors, and others. For this panel, it was determined that expertise was required in toxicokinetics, PBPK modeling, use of uncertainty factors in risk assessment, and experience in overall risk assessment procedures. Along with the appropriate expertise, *TERA* also strives *to* include a range of perspectives on each panel, including diverse professional affiliations (e.g., academic, consulting, environmental, government, and industrial/commercial)[1].

The evaluation of real or perceived bias or conflict of interest is an important part of the panel selection process for both peer review and peer consultation panels. *TERA* makes every effort to avoid selecting panel members with conflicts of interest or with biases that would impair the panel members' scientific objectivity.

For this peer consultation, the following situations were considered to create conflicts of interest for panel members; therefore, *TERA* assured that panel members did not have these situations:

- Working for the sponsor (i.e., *TERA*) of the draft framework document to be reviewed at the peer consultation
- Having financial interests potentially benefiting from the outcome of the peer consultation, or
- Authoring the document

Panel members serve on this panel as *individuals*, representing their own personal scientific opinions. They do not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent their employers or those with whom they are affiliated.

In evaluating situations that may create a potential for bias, *TERA* considered a number of possibilities that may cause an individual to lack the scientific objectivity necessary to

[1] for a more complete discussion of the *TERA* panel formation process, please see http://www.tera.org/peer/PeerProcess.html

review the work product. These included candidates having testified or made public statements regarding the subject matter (i.e., draft framework), or candidates having such strong personal or professional relationship with the authors that they would not be able to objectively review these materials. .The subject of this peer consultation is a draft framework for evaluating whether the default uncertainty factor for human kinetic variability is adequate to protect children. This framework is at an early stage and only preliminary results and conclusions are shown. The results of the peer consultation will be used to conduct further research and development on the uncertainty factor.

None of the panel members has a conflict of interest with this review. Some panel members have recently collaborated with the authors or with the sponsoring organization (i.e., *TERA*) on other projects and efforts, and these are noted. However, each panel member has certified that they have no conflicts of interest and that they are able to objectively evaluate the work product and participate in this peer consultation.

Brief biographical sketches and disclosures for each panel member are found below.

Mr. Harvey J. Clewell III

Mr. Clewell recently joined the CIIT Centers for Health Research as Director of the newly created Center for Human Health Assessment and senior scientist in the Division of Computational Biology. His duties at CIIT include developing a research program on the use of biomonitoring results in exposure and risk assessment. Prior to joining CIIT, Mr. Clewell was a principal scientist for ENVIRON. He has over 25-years of experience in environmental quality research, toxicology research, chemical risk assessment, and hazardous materials management and is a leading expert on the use of tissue dosimetry and mode-of-action information in chemical safety and risk assessment. He is internationally known for his work in the applications of physiologically based pharmacokinetic (PBPK) modeling in cancer and non-cancer risk assessments, and was key to the first uses of PBPK modeling by EPA, ATSDR, OSHA, and FDA.

Mr. Clewell received his B.A. in Chemistry from Bradley University and his M.A. in Physical Chemistry from Washington University. He is a Diplomate of the American Board of Toxicology. Mr. Clewell served for 20 years as an officer in the U.S. Air Force Biomedical Science Corps and was Deputy Director of the Air Force Toxic Hazards Research Unit, Director of Hazardous Materials Safety for the Air Force Aeronautical Systems Center, and consultant to the Air Force Surgeon General on Chemical Risk Assessment.

Mr. Clewell has been involved with the development of a harmonized PBPK model for trichloroethylene, the development of a biologically based dose-response approach for arsenic, the estimation of methyl mercury exposures in U.S. women of child-bearing age using Markov chain Monte Carlo analysis with a PBPK model, the use of PBPK models to consider genetic polymorphisms in risk assessment, the use of PBPK models to address age-specific issues, the development of parameters for PBPK modeling of the neonatal period, PBPK modeling in cancer risk assessment, PBPK modeling of developmental toxicity, and PBPK modeling in pharmaceutical safety assessments. Mr. Clewell has authored numerous scientific publications, has provided testimony in both civil tort cases and congressional hearings, and frequently provides invited lectures and computer workshops in the areas of pharmacokinetics and risk assessment. He has also served on a number of external peer review panels for EPA, ATSDR, and Health Canada.

Mr. Clewell is Adjunct Professor at the University of Louisiana in the Department of Toxicology and is an Adjunct Professor at Colorado State in the Center for Environmental Toxicology and Technology. He is a member of the Society of Toxicology (SOT), Society for Risk Analysis (SRA), and the American Chemical Society.

Disclosure Statement: Mr. Clewell has collaborated with *TERA* on numerous projects, including development of a harmonized PBPK model for trichloroethylene. He also has served on several *TERA* peer review panels. Some of Mr. Clewell's work is cited in the framework document that is the subject of this peer consultation.

Dr. Penelope A. Fenner-Crisp

Dr. Fenner-Crisp recently retired from her position as the Executive Director of the International Life Sciences Institute's (ILSI) Risk Science Institute (RSI), one she had held since December, 2000. She has expertise in risk assessment methodologies, risk assessment guidelines, and incorporation of risk assessment into regulatory decisions. She played a key role in the policy guidance for use of Monte Carlo analyses in exposure assessment, the cumulative risk conceptual framework, and implementation of the cancer guidelines as well as many other policies. Dr. Fenner-Crisp has since established a private consulting practice, and counts ILSI among her clients.

Dr. Fenner-Crisp received her B.S. in Zoology from the University of Wisconsin-Milwaukee and her M.A. and Ph.D. in Pharmacology from the University of Texas Medical Branch in Galveston. Her research interests encompassed the fields of neuro and cardiovascular pharmacology. She completed a postdoctoral fellowship in Pharmacology-Morphology from the Pharmaceutical Manufacturers' Association (now Pharma) Foundation in the Anatomy Department of the Georgetown University Schools of Medicine and Dentistry, with an emphasis on reproductive endocrinology.

Dr. Fenner-Crisp came to ILSI from the U.S. Environmental Protection Agency, having served in a variety of capacities over a period of more than 22 years. Through the years she was the Senior Science Advisor to the Director of the Office of Pesticide Programs (OPP), Director of the Health and Environmental Review Division (HERD) of OPPT, the Acting Deputy Director and Deputy Director for OPP, the Director of the Health Effects Division (HED) in OPP, a Special Assistant to the Assistant Administrator for OPPT, a Senior Toxicologist in the Health Effects Branch of the Office of Drinking Water (ODW), and the Manager of the Health Advisory Program for ODW.

Dr. Fenner-Crisp has been involved in many activities of several international organizations. She has participated as an Expert on WHO IPCS working groups for nine years. She served as the lead U.S. Delegate to the OECD's Endocrine Disruptor Testing and Assessment (EDTA) workgroup, the EDTA's Mammalian Validation subgroup, and the Expert Consultation on Acute Toxicity. In April, 2000, she received the Fitzhugh Green Award, for her contributions on behalf of EPA to its international activities.

Dr. Fenner-Crisp is a member of the Society of Toxicology (SOT) and the Society for Risk Analysis (SRA) and the National Capitol Area Chapter of SOT and SRA (NCACSOT and NCAC-SRA). In 1996, she was the recipient of the SRA's first Risk Practitioner award. She has been a Diplomate of the American Board of Toxicology since 1984 and was named to its Board of Directors in April, 2001. She served as a member of the Board of Directors of the Toxicology Forum from 1990-2000, also serving on its Program Planning Committee. She was honored as a Toxicology Forum Fellow at its 2003 Winter meeting.

Disclosure: None

Dr. Gary L. Ginsberg

Dr. Ginsberg is a Senior Toxicologist at the Connecticut Department of Public Health within the Division of Environmental Epidemiology and Occupational Health using toxicology and risk assessment principles to evaluate human exposures to chemicals present in air, water, soil, food, and the workplace. He has expertise with exposure and pharmacokinetic models and their use in risk assessment.

Dr. Ginsberg received his B.S. in Pharmacy from the State University of New York and his Ph.D. in Toxicology from the University of Connecticut. He was a post-doctoral fellow in carcinogenesis/mutagenesis at the Coriell Institute for Medical Research. Prior to the Connecticut Department of Public, Dr. Ginsberg was a Senior Toxicologist for TRC Environmental Corporation where he managed risk assessment and toxicology projects including developing methodologies to evaluate dose route extrapolation of carcinogens for EPA.

Dr. Ginsberg is currently the Project Manager of several EPA cooperative agreement projects. One project is researching the susceptibility differences between children and adults stemming from age-related pharmacokinetic factors and the other is the influence of genetic polymorphisms on susceptibility to toxicants and inter-individual variability.

Dr. Ginsberg is an Assistant Clinical Professor at the Connecticut School of Medicine and an Adjunct Faculty member at the Yale University's School of Medicine. He was the Chair of the Peer Review Committee for USEPA's RfD for Methylmercury. He is a member of the National Children's Health Study, Medicines/Pharmaceuticals Work Group, and the USEPA Federal Advisory Committee on Children's Health Protection.

Dr. Ginsberg is a member of the Society of Toxicology (SOT) and the Society for Risk Analysis. Dr. Ginsberg has been published in the areas of toxicology, carcinogenesis, physiologically-based pharmacokinetic modeling, inter-individual variability and children's risk assessment.

Disclosure Statement: Some of Dr. Ginsberg's work is cited in the framework document that is the subject of this peer consultation

Dr. Dale Hattis

Dr. Hattis is a Research Professor at the Center for Technology, Environment, and Development at Clark University with 30 years experience in quantitative health risk assessment for cancer and non-cancer health effects. He has expertise in human interindividual variability in susceptibility to toxic effects and pharmacokinetic and Monte Carlo simulation modeling.

Dr. Hattis received his B.A. in Biochemistry from the University of California and his Ph.D. in Genetics from Stanford University. Prior to his current position, Dr. Hattis was a Consultant and Research Associate for the Center of Policy Alternatives.

Dr. Hattis has been involved in several U.S. EPA grants for evaluating risks across life stages, age-related differences in susceptibility to carcinogenesis, adult-child differences in pharmacokinetic parameters and inter-individual variability, and pharmacokinetic modeling for local site-acting carcinogens.

Dr. Hattis is a member of the Environmental Health Committee of the EPA Science Advisory Board, the Food Quality Protection Act Science Review Board, and participated in the review of the EPA RfD for boron. In the past, Dr. Hattis has served on review committees for EPA, National Toxicology Program, National Academy of Sciences/Institute of Medicine, National Research Council, the US Food and Drug
Administration, OSHA, Natural Resources Defense Council, State of California, and the International Life Sciences Institute.

Dr. Hattis is a member of the Society for Risk Analysis (SRA) and has served as a Councilor. He was awarded a fellow from SRA in 2000. He is a member and is a past president for the New England Chapter of the SRA. Dr. Hattis is a member of the editorial board for *Risk Analysis*. Dr. Hattis has been published in the areas of pharmacokinetic modeling, toxicology, dosimetric scaling, genetic polymorphisms, and risk assessment.

Disclosure Statement: Some of Dr. Hattis' work is cited in the framework document that is the subject of this peer consultation.

Ms. Ann Marie Jarabek

Ms. Jarabek is currently a U.S. EPA Visiting Scientist in the Department of Computational Biology at the CIIT Centers for Health Research. Via this assignment, she is working on a joint project to develop value-of-information (VOI) analyses as a means to inform uncertainty factors applied for intrahuman and interspecies extrapolation. The approach will focus on formalizing confidence in mechanistically based model descriptions of dosimetry and tissue reactions for inhaled irritant gases.

Ms. Jarabek received a B.S. in biology from the University of Notre Dame and trained in inhalation toxicology at the University of Cincinnati Medical Center. She is currently pursuing additional studies in biomathematics at institutions in the RTP. Ms. Jarabek is the principal author of the EPA's methods to derive inhalation reference concentrations (RfCs) that incorporate dosimetry modeling of inhaled particles and gases to improve characterization of dose.

Her most recent EPA research involved developing mode-of-action dosimetry models for the inhalation, oral, and dermal routes. As a Senior Toxicologist and Special Assistant to the Associate Director for Health in the National Center for Environmental Assessment, Ms. Jarabek represented the Agency on a number of public-private partnership steering committees that developed case studies for the application of mode of action information per the 1996 proposed cancer assessment guidelines, she also consults on committees evaluating how to harmonize approaches of noncancer and cancer and on the use of biomarkers in risk assessment. She also contributed to the practice of using dosimetry modeling for route-to-route extrapolation, and technical reviews and negotiations to use pharmacokinetic data to inform alternative testing strategies. She was involved with implementation of the benchmark dose approach for dose-response modeling and developed a Bayesian application that provides for statistical combination of dose-response estimates and allows for calculation of risk above reference levels, which was recently extended to combine health and ecotoxicological risks.

Ms. Jarabek is active in the National Occupational Research Agenda, the Society of Toxicology (SOT) and the Society for Risk Analysis (SRA). She has been an elected councilor to SRA and continues to serve SRA on the annual meeting program and workshop committees. She has received four awards for outstanding presentation from the Risk Assessment Specialty Section of the SOT, plus an award for best manuscript demonstrating a risk assessment application in 2001. She was elected in 2002 to serve a four-year term as an officer of the Risk Assessment Specialty Section of the SOT and is currently presiding as its President for 2004-2005.

Ms. Jarabek has received one silver and four bronze medals for her work in the Agency, and has provided invited presentations on dosimetry methods, mode of action, and statistical considerations for dose-response assessment to the National Academy of Sciences (NAS), the Science Advisory Board (SAB) of EPA, the Toxicology Forum, and the EPA’s Risk Assessment Forum.

Disclosure Statement: Ms. Jarabek has served on a previous peer review panel organized by *TERA*. Some of Ms. Jarabek’s work is cited in the framework document that is the subject of this peer consultation.

Dr. Kannan Krishnan

Dr. Krishnan is a Professor of Occupational and Environmental Health at the University of Montreal (Canada) where he has been the Director of the Human Toxicology research group (TOXHUM). He provides leadership to the group and defines the research vision for the team. He is an expert in the areas of pharmacokinetics, PBPK modeling, mixture toxicology, and health risk assessment methods.

Dr. Krishnan received his B.Sc. in Agriculture form Annamalai University (India), his M.Sc. in Toxicology and Environmental Chemistry from McGill University and his Ph.D. in Public Health for the University of Montreal. Dr. Krishnan is currently researching computer modeling in health risk assessment, toxicokinetics and physiologically-based toxicokinetic modeling, quantitative structure-activity relationship (QSAR) models for risk assessment, adult-to-children extrapolation of tissue and exposure doses of chemicals, and risk assessment approaches for chemical mixtures.

Dr. Krishnan has been a peer reviewer of several IRIS updates, risk assessments, mixture risk assessment supplemental guidance and efforts on interactions for US EPA. He has also been actively involved as a reviewer of documents on toxicological profiles of chemicals, interaction profiles involving environmental contaminants and mixture risk assessment guidelines for ATSDR.

Dr. Krishnan was the leader of the risk assessment methodologies theme team of the Canadian Network of Toxicology Centres and Vice President of the Biological Modeling Specialty Section of the Society of Toxicology. He is a member of the U.S. National Academy of Sciences (NAS) Sub-committee on Acute Exposure Guideline Levels and is currently the vice-president of the Risk Assessment Specialty Section of the Society of Toxicology (SOT), member of the scientific programme committee of the Society of Toxicology and a temporary advisor for the World Health Organization for developing a scientific document on the principles for evaluating health risks in children associated with chemical exposures.

He has been on the editorial boards of *Toxicological Sciences*, *International Journal of Toxicology*, *Journal of Applied Toxicology*, and *Journal of Child Health*. He's an author of a text book on environmental pollution, and has authored or co-authored over 90 full-length publications in the areas of QSAR modeling, PBPK modeling, chemical mixtures, and health risk assessment.

Disclosure Statement: Dr. Krishnan has served on peer review panels organized by *TERA*. Some of Dr. Krishnan's work is cited in the framework document that is the subject of this peer consultation.

Dr. John Lipscomb

Dr. Lipscomb is a toxicologist with the U.S. EPA, Office of Research and Development, National Center for Environmental Assessment. His responsibilities at the agency involve the development and assessment of refined risk assessment methods, including evaluation of toxic mechanisms of action, dose-response assessments, exposure quantifications, and definitions of intrinsic modifiers of toxicity. He also reviews methods and guidelines related to the toxicological effects of environmental pollutants.

Dr. Lipscomb received his B.S. and M.S. degrees in Biology from the University of Central Arkansas and his Ph.D. degree in Interdisciplinary Toxicology from the University of Arkansas for Medical Sciences. Prior to joining EPA, he served as Captain in the U.S. Air Force and Chief of the Metabolism Section in the Toxicology Division of the Armstrong Laboratory at Wright-Patterson Air Force Base. While in that assignment, he designed and conducted research in xenobiotic metabolism in response to Air Force environmental and occupational health needs, determined the enzymological basis for human inter-individual and species-dependent differences in bioactivation, and identified potential modifiers of toxicity.

Dr. Lipscomb currently is Adjunct Assistant Professor in the Department of Therapeutics, College of Pharmacy, University of Cincinnati, and also in the School of Public Health and Tropical Medicine, Department of Biological Sciences, Tulane University. He has been a Diplomate of the American Board of Toxicology since 1995.

Dr. Lipscomb is a member of the Society of Toxicology, the Society for Risk Analysis, and the International Society for the Study of Xenobiotics. He also is past and present office-holder in the regional chapters and specialty sections of these organizations. He has received numerous achievement awards and medals from the U.S. Air Force, Army, EPA and the National Institute for Occupational Safety and Health. In 2000, 2002 and 2003 he received awards from the SOT Risk Assessment Specialty Section for Outstanding Poster and Platform Presentations, Best Abstract, and Top Ten Best Papers.

Disclosure Statement: Dr. Lipscomb is the EPA Project Officer for two reports that are being written (under contract) by *TERA* scientists regarding noncancer risk assessment processes and identifying sensitive subpopulations for risk assessment.

Dr. Lisa M. Sweeney

Dr. Sweeney is a Program Manager at The Sapphire Group, where her responsibilities include the development and refinement of physiologically-based pharmacokinetic (PBPK) models and their application to risk assessment. She has a broad range of experience in the application of toxicology, chemistry, and engineering to problems in the health and environmental sciences. Dr. Sweeney has over 10 years experience in risk assessment, pharmacokinetics, and biochemical engineering from a variety of private sector and non-profit backgrounds.

Dr. Sweeney received her B.S.E. in Chemical Engineering from Case Western Reserve University and her Ph.D. in Chemical Engineering with a minor in toxicology from Cornell University. She worked as a research engineer for Amoco Corporation, where she established a research program on the biological effects of contaminated soil and water and designed experiments to enable ecological and human health risk assessments. She also was a team member of the Industrial Health Risk Assessment program at Concurrent Technologies Corporation where she led efforts to support three Department of Defense manufacturing or maintenance facilities.

Dr. Sweeney is currently managing a High Production Volume (HPV) toxicology data review for glycol chemicals. This work involves development of robust summaries, the test plan, and the SIDS Initial Assessment Report. Dr. Sweeney has been involved in the development of workplace exposure limits for glycol ethers. It has included identifying critical NOELs from animal studies, developing PBPK models of the chemicals' disposition in animals, men, and pregnant women, and using equivalent internal dosimetry and uncertainty factors derived from Monte Carlo simulation as the basis for scientifically-defensible workplace exposure limits.

Dr. Sweeney is a member of the Society of Toxicology, the Society for Risk Analysis, and several other professional organizations. In 2003, she was the recipient of the SOT's Risk Assessment Specialty Section award for Outstanding Paper Demonstrating an Application of Risk Assessment. She has been a Diplomate of the American Board of Toxicology since 1998 and is a Certified Hazardous Materials Manager.

Disclosure: None.

Author Biographical Sketches

Dr. Lynne Haber

Research Program Manager
Toxicology Excellence for Risk Assessment *(TERA)*

Dr. Lynne Haber has 14 years of experience in developing human health risk values for a variety of government agencies and private sponsors, and in research related to risk assessment methods. Dr. Haber is *TERA*'s Research Program Manager, and was the program leader for *TERA*'s chemical-specific assessment program (*VERA*, Verifiable Estimates for Risk Assessment) for 2 years. As program manager, she provides overall direction for the program, leads marketing efforts, and provides oversight for research projects.

Dr. Haber received her B.S. in chemistry from U.C.L.A., and her Ph.D. in molecular biology from M.I.T. Prior to joining *TERA* she worked for ICF/Clement, also focusing on work developing human health risk values.

Her interests include the improved use of mechanistic data in risk assessment, including incorporation of mode of action data in cancer risk assessment, and use of data to replace default uncertainty factors. Dr. Haber is active in communicating her findings to the broader scientific community through participation in professional societies, teaching courses in risk assessment methods, routine publication of her work, service as an editorial reviewer for scientific journals, and through presentation of invited lecturers.

Dr. Haber is a member of the Society of Toxicology (SOT) and the Society for Risk Analysis (SRA). She served as vice president and councilor of the SRA Dose-Response specialty group, and is a Diplomate of the American Board of Toxicology (DABT).

Dr. Haber has been the lead author, coauthor, or reviewer of dozens of detailed assessment documents (including oral and inhalation noncancer and cancer values) using state of the science risk assessment methods. Her work includes documents for EPA's Integrated Risk Information System (IRIS) and EPA program offices (including Drinking Water Criteria Documents and Health Advisories), for other government agencies (e.g., ATSDR and DOD), and for private sponsors. She has served as a panel chairperson or panel member for scientific peer reviews organized by *TERA*, EPA, and other U.S. and foreign government agencies. She has also served on two panels for the NAS/NRC.

Dr. Haber's published work includes lead authorship of the chapter on noncancer risk assessment (including dose-response modeling methods) for Patty's Toxicology, and an invited review on the use of mechanistic data in risk assessment. She was the coauthor for an analysis of the effect of genetic polymorphisms on human variability in dose, using PBPK and Monte Carlo modeling. She has also published on methods deriving occupational exposure limits, and on incorporating toxicokinetic data into risk assessment.

Mr. Eric Hack

Biomathematician
Toxicology Excellence for Risk Assessment *(TERA)*

Mr. Eric Hack has 6 years of experience with quantitative human health risk assessment methods. As *TERA*'s biomathematician, he provides mathematical modeling and analytical support to risk value development and risk assessment methods research projects.

Mr. Hack received a B.A. in mathematics from Western Kentucky University, and a M.S. in environmental science from the Air Force Institute of Technology. Prior to joining *TERA*, he was part of the Crump Group and Environ International, working to develop human health risk values and risk assessment methods.

Mr. Hack's interests include mathematical modeling of the responses of biological systems to chemical exposures and analysis of such models to evaluate and reduce uncertainty in risk estimates. He is experienced with physiologically-based pharmacokinetic modeling and pharmacodynamic or biologically-based dose-response modeling. He is also interested in the use of hierarchical population models and Bayesian statistical methods to analyze uncertainty in model predictions.

Mr. Hack has authored or coauthored scientific documents regarding the modeling of chemical kinetics in humans and animals and the statistical analysis of such models. Projects particularly related to inter-human variability or uncertainty include an analysis of the variability in human dose metrics due to genetic polymorphisms, and an analysis of uncertainty and variability in mercury intake using a physiologically-based pharmacokinetic model and Markov chain Monte Carlo analysis.

Dr. Jay Zhao

Toxicologist
Toxicology Excellence for Risk Assessment *(TERA)*

Dr. Jay Zhao has 7 years of research and teaching experience in environmental toxicology and tumor epidemiology, as well as 8 years of experience in chemical risk assessment at *TERA*. Dr. Zhao has strong and diverse training in medicine, public health, and toxicology. He has been the project lead on numerous projects and the principle author of various articles.

Dr. Zhao received his medical degree and M.P.H. from Shanghai Medical University, China, and his Ph.D. in toxicology from the University of Cincinnati. Prior to joining *TERA*, Dr. Zhao had research and teaching experience in environmental toxicology, especially in mutagenicity studies on air and water pollutants. He played a leading role in many research projects, such as mutagenicity evaluation of water pollutants, indoor and outdoor air pollutants, biomonitoring of human mutagen exposure, evaluation of mutagen removal efficiency from water, and tumor epidemiology.

Dr. Zhao has managed and participated in preparing numerous risk assessment documents for government agencies, such as EPA's Integrated Risk Assessment System (IRIS), EPA's Office of Water, and the National Institute for Occupational Safety and Health (NIOSH). As a project leader and principal author, he managed and prepared the Drinking Water Summary Document for Cyanobacterial Toxins for the U.S. EPA and Office of Water (EPA/OW) and also the Toxicological Review of Decabromodiphenyl Ether for IRIS. He was the lead author of a Drinking Water Support Document on Aldicarb and Related Compounds and a principal author of Trimethylbenzene Toxicity Profile for EPA/OW. He also was a co-author of several other risk assessment documents for U.S. EPA such as: Drinking Water Criteria Document for Chlorinated Haloacetic Acids, Toxicological Review of Soluble Nickel Salts, Toxicological Review of Phenol, Relative Source Contribution for Chloroform, and Benchmark Dose and Categorical Regression Modeling for Chloral Hydrate. As a project leader and principal author, he also managed and prepared occupational hazard profiles of five chemicals for NIOSH.

In addition to chemical risk assessment, Dr. Zhao has extensive experience in dose response modeling. His main interest in chemical risk assessment is quantitative analysis of dose response, including dose-response modeling, chemical mixture toxicity, chemical-specific adjustment factors (CSAF), and uncertainty analysis. He developed hands-on training courses on Benchmark Dose (BMD) Modeling and Dosimetry in Risk Assessment, and successfully conducted training on these subjects for toxicologists at the National Sanitation Foundation in 2002, and for staff in the Texas Commission on Environmental Quality in 2004. Most of this material has been used by the EPA's BMDS task manager for workshops at recent Society of Risk Analysis (SRA) and Toxicology and Risk Assessment Conferences. Dr. Zhao is a member of the Society of Toxicology (SOT) and Chinese Society of Toxicology.

APPENDIX C

Author Presentation Slides

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Draft Conceptual Framework for Evaluating Adult-Child Kinetic Differences

Eric Hack
Lynne Haber
Jay Zhao

Toxicology Excellence for Risk Assessment (*TERA*)

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Purpose

- Sufficiency of UF_{HK} for protecting children
- How to judge without a PBPK model?
- Consolidation/organization of existing data
- Factors driving the kinetics?
  - How is answer affected by chemical properties
- Identify situations most likely of concern
- Focus data collection efforts and further analyses

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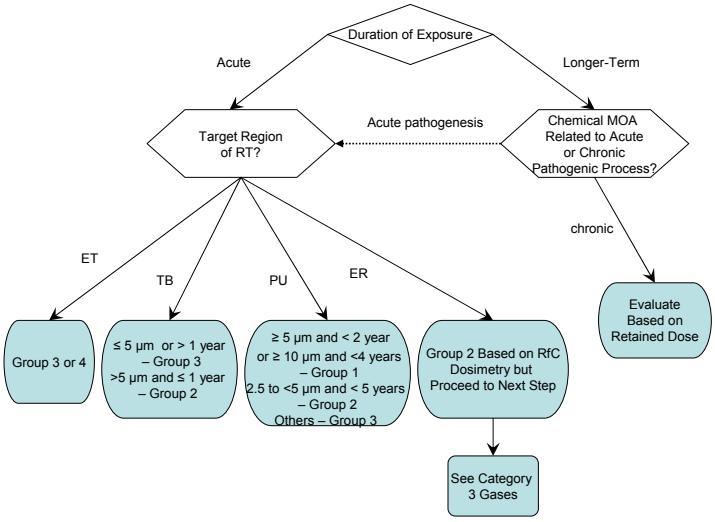
What It Is Not

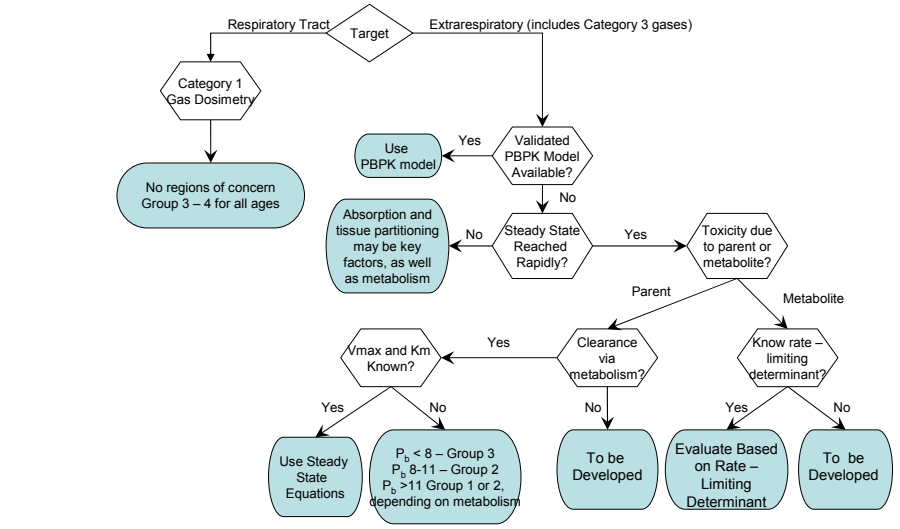
- Reproductive/developmental endpoints
- Fetal toxicokinetics
- Differences in exposure patterns
- Toxicodynamic differences

Conceptual Framework - Particles



Group 1 = Of concern. A factor of 3.2 does not appear to be sufficient.
Group 2 = Interindividual variability needs to be considered. The estimated ratio falls between 2 and 3.2
Group 3 = Not of concern. The calculated ratio is between 1 and 2.
Group 4 = Children are estimated to receive a lower dose than adults.

Conceptual Framework - Gases



Group 1 = Of concern. A factor of 3.2 does not appear to be sufficient.
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Group 4 = Children are estimated to receive a lower dose than adults.

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Exposure Duration Considerations

- Acute exposures
- LADD and period of increased dose
- Window of susceptibility (toxicodynamics)
- At steady state throughout most of the exposure

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Analysis

- Inhalation dosimetry
  - Particle and gas exposure
- Oral dosimetry
  - To be developed
- Dermal dosimetry
  - To be developed

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Inhalation Dosimetry

- Particle dosimetry approach
  - RfC methodology with age-dependent parameters
- Category 1 gas dosimetry approach
  - RfC methodology with age-dependent parameters
- Category 3 gas dosimetry approach
  - Age-dependent partition coefficients
  - PBPK-based steady state equation
  - Bounding estimates

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Possible Future Enhancements

- Intra-age variability
- Inhalation dosimetry
  - ICRP model (Ginsberg 2005)
  - MPPD model (new release coming, Asgharian 2004)
  - Particle clearance
  - Category 2 gases
  - Systemic kinetics of inhaled particles
- Other bounding estimates

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Possible Future Enhancements

- Extrahepatic elimination
- Oral exposure
- Non-steady state analysis
- Generalize PBPK results for further categorical definition


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Questions?