Report of the Peer Consultation on a Draft Framework to Evaluate Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals

August 7, 2007

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

May 9, 2008

Note

This report was prepared by scientists of Toxicology Excellence for Risk Assessment (*TERA*) as a summary of discussions and conclusions from a peer consultation meeting. The members of the peer consultation panel served as individuals, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

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Introduction and Background

An expert panel met on August 21, 2007, to conduct a scientific peer consultation of a document titled the "Draft Framework to Evaluate Adult-Child Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals." The subject document was prepared by a team of scientists, including Lynne Haber of Toxicology Excellence for Risk Assessment (*TERA*); Kannan Krishnan from the Université de Montréal; and, Robinan Gentry of ENVIRON.

The authors built upon an earlier framework proposed by *TERA* scientists and discussed by the same group of experts in March 2005. This initial framework document was prepared by Lynne Haber, Eric Hack and Jay Zhao of *TERA*. In 2005 the expert panel recommended that the framework be restructured and that tissue dose be compared, rather than adequacy of the uncertainty factors. This revised framework and documentation package presents an analytical approach for evaluating relative tissue dosimetry in adults and children for inhaled gases. The authors prepared case studies to provide perspective on the potential range of internal dose in children and adults for different combinations of physicochemical characteristics and active form. The documentation provides screening-level information on relative dose to children versus adults. The document is intended to serve as an aid to risk assessors to identify the parameters and chemical characteristics that result in children receiving a different dose from adults (higher or lower).

This peer consultation meeting was organized by Toxicology Excellence for Risk Assessment (*TERA)* with support from the U.S. Environmental Protection Agency (Cooperative Agreement CX-82916801) and *TERA* in-house funds. *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 health risk assessments. This meeting was a peer consultation, organized for the purpose of providing expert input and advice regarding the subject report. The objective of this peer consultation was for a diverse group of appropriate experts to review the subject document and provide individual opinions on the merit and adequacy of the proposed approach. In order to maintain separation and independence between the development of work product and its review, 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* asked the original members of the March 2005 panel to participate in this peer consultation of the revised framework and documentation. See http://www.tera.org/peer/adultchildtk/actkwelcome.htm for more information and a report of the March 2005 peer consultation. *TERA* staff evaluated whether panel members had conflicts of interest or biases that would interfere with their objectivity for this review and determined that none were conflicted or biased.

Participants

Authors

Dr. Lynne Haber, Toxicology Excellence for Risk Assessment (*TERA*)

Dr. Kannan Krishnan, Université de Montréal

Ms. Robinan Gentry, ENVIRON

Panel Members[1]

The original members of the March 2005 panel were asked to review the revised framework and documentation. The following individuals participated in the August 2007 peer consultation:

Dr. Harvey Clewell III, DABT, Physical Chemistry
Center for Human Health Assessment, CIIT Centers for Health Research

Dr. Penelope Fenner-Crisp, DABT, Pharmacology
Private Consultant

Dr. Gary Ginsberg, Toxicology
Connecticut Department of Public Health

Dr. Dale Hattis, Genetics
Clark University

Ms. Annie M. Jarabek, Biology / Inhalation Toxicology
U.S. EPA Visiting Scientist
Division of Computational Biology, CIIT Centers for Health Research

Dr. John Lipscomb, DABT, Toxicology
U.S. Environmental Protection Agency

Dr. Lisa Sweeney, DABT, Chemical Engineering/Toxicology
The Sapphire Group

Facilitator

Dr. Andy Maier of *TERA* facilitated the conference call meeting.

[1] Affiliations listed for identification purposes only. Panel members served as individuals on this panel, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

Public Comments

Public comments were received from two individuals, Anthony Carpi, Associate Professor of Environmental Toxicology at the John Jay College of Criminal Justice and Dr. Ernest V. Falke, of the U.S. EPA's Acute Exposure Guideline Levels Program. Mr. Capri strongly recommended that the authors include mercury in their "reevaluation as it is often overlooked, but it is a volatile, highly toxic, and relatively common inhalation exposure risk." Dr. Falke provided detailed comments and suggestions for improving the text, and asked a number of questions. Copies of the complete comments are available upon request (*TERA*@tera.org).

Author Presentation

The meeting began with Dr. Lynne Haber, one of the document authors, summarizing the revised framework document. She stressed that although the ideal approach to understanding age-dependent dosimetry differences requires physiologically based pharmacokinetic (PBPK) modeling, 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, and to aid in prioritizing chemicals for more detailed analyses. She presented a schematic diagram of a conceptual framework for evaluating age-dependent dosimetry differences for gases and vapors. The effort focused on systemically-acting chemicals. For scenarios where steady-state assumptions apply, equations were developed to estimate child-to-adult differences in tissue dose, depending on whether the toxic moiety is the parent chemical, a reactive metabolite, or a stable metabolite. Application of these equations was demonstrated using both simplifying assumptions and case studies for which PBPK models were available. Appendix A contains a copy of the presentation slides.

Panel Discussion and Recommendations

Following the presentation, the panel discussed key aspects of the document as highlighted in the charge to the panel. The deliberations of the panel were supplemented by input from the document authors. Their discussions and comments addressed the following nine charge questions:

1. Does the overall framework diagram (Figure 1) make sense and is it useful for comparing inhalation dosimetry of gases in adults and children? Are there additional differentiations that should be captured and considered? Specifically, please comment on the scientific soundness and defensibility of the approaches used to:
    a. Differentiate the "acute" vs. chronic branches
    b. Address steady state vs. non-steady state conditions
    c. Address portal of entry effects
    d. Address systemic toxicity caused by the parent, a stable metabolite, and a reactive metabolite
2. Please comment on the considerations for application of the chronic branch of the framework and when it would be relevant. Are there other considerations that should be added to make the framework more relevant to chronic exposure, or other considerations

that should be mentioned? Given the considerations listed for application of this branch, is there a better term for the relevant duration?
3. Was the key literature adequately covered in the background portion and discussion? Are there additional studies that should have been considered?
4. Do the steady state equations appropriately characterize the dose metrics being calculated? Were appropriate values used for the parameters for children and adults. Are the results sound and do they provide a reasonable estimate of the maximal magnitude of adult-child differences? Have all the important limitations and uncertainties for the analyses and results been identified and discussed?
5. The authors verify their bounding analyses results by comparing them with PBPK modeling results. Have they made appropriate comparisons and do you agree with their conclusions?
6. The framework approaches the analysis by target area (portal of entry vs.systemic), and presents steady state analyses for Category 3 gases (systemic effects). The framework notes that the approaches for Category 2 gases would be along the lines described for Category 1 gases (for portal of entry effects) or for Category 3 gases (for systemic effects), but that the steady state calculations presented may not be completely accurate for systemic effects of Category 2 gases. However, a verification analysis found reasonable results for one Category 2 gas (isopropanol). Is further explicit consideration of Category 2 gases needed?
Are there modifications that should be made to the steady state equations for Category 2 gases?
7. Was the document transparent? Are the assumptions and data presented completely and clearly?
8. The authors indicate that the framework and analyses present an analytical approach for evaluating the relative tissue dosimetry in adults and children for inhaled gases. The results of such analyses could be used to aid risk assessors in identifying the parameters and chemical characteristics that result in children receiving a higher tissue dose for a particular chemical. Do the analyses and information presented provide adequate support for the use of the framework and results in this fashion? Are there conditions or situations when the framework should not be used?
9. Do you have further comments or suggestions for this report or for the framework and the overall approach?

Individual panel members made recommendations for enhancement and revision of the framework and documentation. These recommendations are summarized below. Note that the recommendations reflect individual opinions; there was no attempt to reach a group consensus at this stage. As appropriate, individual panelists identified and discussed disagreements during the course of the discussions.

General Recommendations Related to the Overall Framework Design and Description

Panelists suggested numerous revisions to Figure 1 to cover the considerations required to evaluate whether the chemical is systemically acting, is likely to reach steady state or have a

specific window of vulnerability, and the impact of toxicodynamic issues that affect assumptions about exposure durations of interest.

- The initial diamond in Figure 1 (Exposure Duration, Mode of Action, Nature of Effect) needs to elaborate on the importance of mode of action and use of toxicity data to identify toxic moiety, as well as consideration of reversibility and window of vulnerability. The figure should then follow two branches depending upon whether steady state was reached for the dose metric of interest. The term Toxicity should replace Exposure Duration.
- Some suggested that rather than merely expanding the initial diamond entry point of the figure, a decision tree (Figure 1a) should be included and address toxicodynamics, dose metric, window of vulnerability and reversibility. The corresponding text needs to be expanded to further explain when one needs to use a toxicokinetic model and when the simple steady state equations are appropriate.
- The text should clearly define steady state and assumptions for steady state.
- If the conditions are such that the chemical will not reach steady state, the non-steady state branch would recommend modeling in order to estimate the tissue dose for the appropriate toxic form or dose metric for adults vs. children.
- The framework needs to make it more clear that it addresses child/adult dosimetry and the figure should link steady-state equations to a table of specific parameters and the issues relevant to assessing child: adult differences.
- Some panelists thought that the portal of entry oval in Figure 1 should be removed because these types of effects are not covered by this framework. Others thought it could be left in but marked in some way and the text should clearly explain that the framework and document do not address it.

Other Technical Comments and Recommendations

Many of the panel encouraged the authors to put the assumptions and parameter values used into tables to make it easier for the user to identify and understand the values and assumptions used. This would also help streamline the documentation and provide the user with a sense for how extensive or lean the literature is. Enough information should be provided so that the user can trace each value back to its source. Additional information should be provided from the original literature to capture the uncertainty and variability in the studies. More information and data on the underlying data used for the worked examples is also needed. The document needs to clearly state whether values are point values or estimated from regression and what difference that might make.

Panel members discussed the steady state equations and made a number of suggestions:

- The text should clearly caveat that not all cases or situations are covered, for example the situation when a reactive metabolite is produced in an organ other than the liver and acts locally. It should be made clear that the steady state equations did not capture variability.
- Expand the discussion and details on renal and pulmonary clearance
- Emphasize that the analyses are based on the arithmetic means of the various parameters. Information on variability, such as error bars in results and/or variability in parameters (e.g., in a table) would be useful.

- The weakest part of the steady state calculation is the final case study, for which the toxic moiety is a stable metabolite cleared efficiently in adults (i.e., flow limited process) but not at all in children (i.e., where there is both age-dependent formation and clearance of the toxic form via both metabolism and renal clearance). This document highlights the importance of differential ontogeny for toxic metabolites.
- The document should be clear that the equation for the steady state concentration of reactive metabolite (Equation 3) does not cover all possible scenarios of metabolite generation and reactivity. .

Panel members noted that the bounding exercises were well-done but the document needs to make it clear that this is a simplistic approach that is intended to help identify problems and highlight concerns during the problem formulation stage. It needs to be made explicit that this is not bounding of the parameter values. The assumptions, terms used in equations and derivation of values for the bounding exercises need to be clarified.

The document should more clearly articulate the category scheme used by EPA for gases, and clarify that the categories are not based on inherent properties of gases, but strategies for identifying model structure. Panel members agreed that the text on Category 2 (section 2.2) should be removed because once the chemical reaches steady state it does not matter if it is Category 2, and the Category 3-type approach works.

The panel members discussed the appropriate use or application of the framework. They noted that it would be useful during the problem formulation step to identify areas of concern or as a screening tool, but it is not appropriate for quantification. It could be used to inform concerns regarding adequacy of the uncertainty factor for human variability. One panel member suggested clarifying that the document focuses on chemicals that are volatile and reach steady state.

Panel members made a number of additional suggestions:

- The text needs to note key metabolic pathways that are important in children but not adults (or vice versa).
- Discuss blood:air and tissue:blood partition coefficients as a function of age, citing literature from Mahle and Rodriguez.
- It would be helpful to incude a discussion on the issue of the novel or low percent of pathways that are important in children but not adults.
- The framework needs to consider body weight scaling and the implications of the parent versus the metabolite. It is mentioned in the literature that this scaling relates to dose metric. This should be discussed and how scaling is reflected in parameter values.
- Clarify that what is presented in the case studieswith the hepatic extraction set to zerois a worst case scenario, but note whether this is supported by data and what those data are. Be careful in explaining this to prevent readers from taking this out of context.
- Panel members suggested additional literature that the authors could include, and some panelists encouraged inclusion of secondary analyses.

Attachment 1 - Author Presentation Slides

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Draft Framework to Evaluate Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals

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History and Rationale of Project

- 2005 – Initial draft and Peer Consultation on adequacy of intraspecies uncertainty factor to protect children
  - Panel restructuring of framework
  - Recommendation to compare tissue dose rather than adequacy of uncertainty factor
- 2007 – Revised draft and Peer consultation
  - Gases only, focus on systemic effects of VOCs
  - Comparison of mean dose to adult and child, rather than adequacy of UF
  - Added case studies, bounding analyses, and comparison with literature for steady state conditions

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Framework Authors

- 2005 Draft:
  - Lynne Haber
  - C. Eric Hack
  - Jay Zhao
- 2007 Draft
  - Lynne Haber - *TERA*
  - Kannan Krishnan - Université de Montréal
  - Robinan Gentry - ENVIRON

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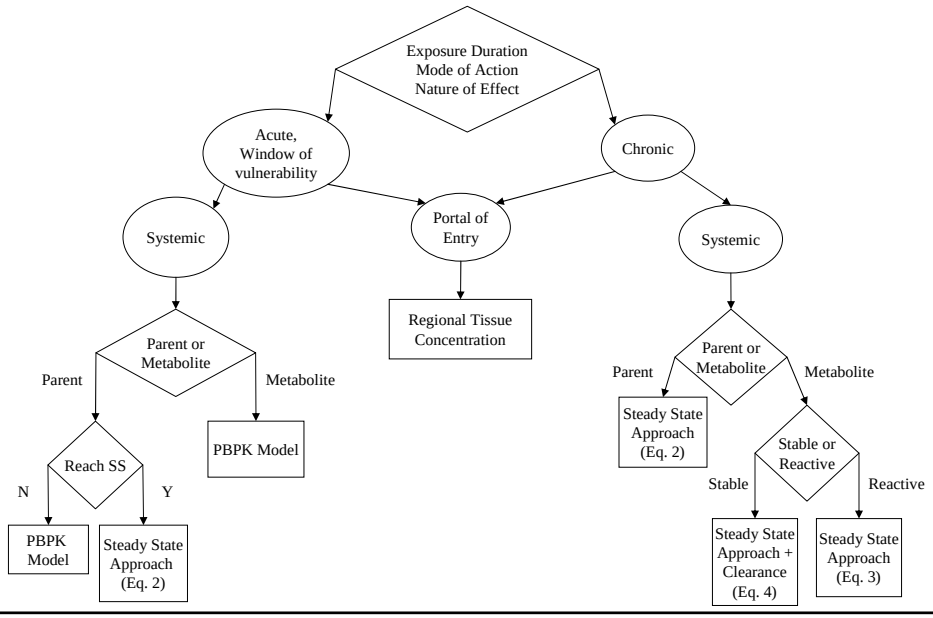
Purpose of the Document

- Provide an analytical approach for evaluating the relative tissue dosimetry in adults and children for inhaled gases
- Provide perspective on the potential range of internal dose of parent or metabolite in children and adults for various combinations of physicochemical characteristics and active form
- Provide screening-level information that can be used in assessments on relative dose to child vs. adult
- Aid risk assessors in identifying the parameters and chemical characteristics that result in children receiving a higher (or lower) internal dose than adults.
- Stimulate further data collection and more in-depth analyses

Revised Framework for Evaluating the Relative Tissue Dosimetry in Adults and Children for Inhaled Gases



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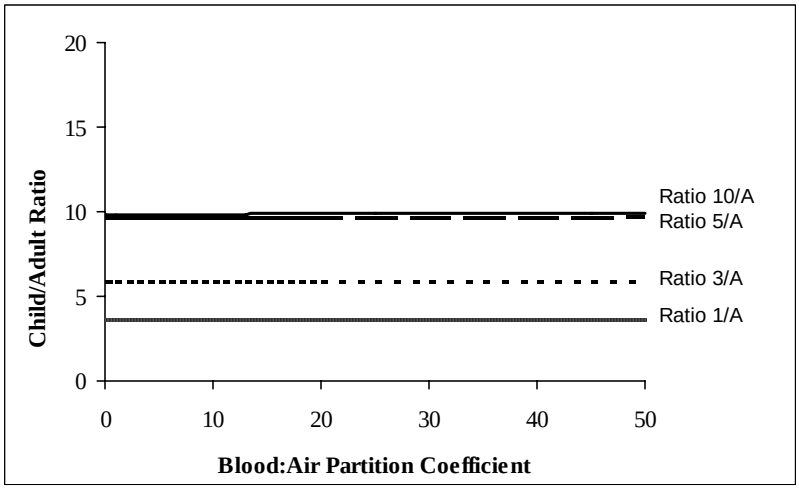
Conditions Addressed – All at Steady State

- Active form of chemical
  - Parent
  - Reactive metabolite
  - Stable metabolite
    - Stable metabolite that is cleared by metabolism
- Metabolic capacity of child
  - Bounding – no hepatic extraction, only renal clearance
  - Bounding – flow-limited clearance, hepatic extraction same in adult and child
  - Hepatic extraction reflects age-specific development of enzyme levels – CYP2E1 and ADH

(Fig. 13) Flow-limited clearance of stable metabolite in adults, only renal clearance in children (CLint of parent = 0.1 L/hr)



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Assumptions and Considerations

- "Chronic" is defined by having reached steady state
- Extra-hepatic metabolism does not contribute significantly to clearance (framework addresses *total* clearance, but case studies were more limited)
- Does not include protein binding
- Does not include age-related differences in Phase II metabolism

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Verification - #1

- Compared results with similar analyses conducted using PBPK models for a range of chemicals
  - Parent chemical, highly metabolized gas – within factor of 2.1
    - Furan – 1.5 (Price et al. 2003); styrene – 1.8, vinyl chloride 1.13 (Sarangapani et al. 2003); 1.75 – Ginsberg et al. (2005)
  - Parent chemical, poorly metabolized gas – ratio ~1
    - Perchloroethylene – 1.02 (Sarangapani et al. 2003)

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Verification - #2

- Reactive metabolite – highest ratio when flow limited metabolism – 1.45
  - Vinyl chloride – 1.34, styrene – 1.83(Sarangapani et al. 2003)
- Reactive metabolite, low intrinsic clearance – ratio becomes much smaller than 1
  - Perchloroethylene – 0.27 (Sarangapani et al. 2003)
- Stable metabolite that is cleared efficiently in adults, but not in children – ratio can get large
  - Acetone metabolite of isopropanol – 7-9 (Sarangapani et al. 2003)

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Conclusions

- Framework provides an approach to thinking about relative dose to child and adult
- Steady state equations provide estimates of relative dose for common industrial chemicals similar to those obtained using sophisticated models
- These equations can provide rough estimates of relative dose for other chemicals with key data (partition coefficient, active form, metabolic pathway)
- The broader framework and equations can be enhanced with additional chemical-specific information when appropriate

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Questions?